Compliance Program Guidance Manual

Inspection of Source Plasma Establishments - 7342.002

Implementation Date:	December 1, 2004
Completion Date:	September 30, 2008
Product Codes:	57DY[] [] – Source Plasma 57DY[] [] – Source Leukocytes 57DI – Further mfr. (In Device/Device Components) 57YY [] []– Miscellaneous Biologics
Programs/Assignment Codes:	42002 Source Plasma 42002A Pre-License 42832 Pre-Approval 42R825 AIDS Related Activity

---

FIELD REPORTING REQUIREMENTS

A. General

Districts should send Establishment Inspection Reports (EIRs) that contain issues requiring policy development or clarification or questions concerning inspection issues to the Center for Biologics Evaluation and Research (CBER) for review. Send the EIR and relevant exhibits electronically, if possible, to cberinspections@cber.fda.gov, or by mail to the following address:

Division of Inspections and Surveillance (HFM-650)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200 N
Rockville, MD 20852-1448

B. Fatality Follow Up

Send a copy of the relevant sections of the EIR with exhibits pertinent to the fatality to the Fatality Program Manager (HFM-650) at the general address above or electronically to the point of contact that issued the inspection follow up assignment.

Report a product collection-related fatality found during an inspection, to the Fatality Program Manager, at 301-827-6220.

C. Warning Letters to Blood Establishments

Send a copy of the Warning Letter and any correspondence between the firm and the District Office, to the Chief Blood and Tissue Compliance Branch, Division of Case Management (DCM) at the general address above. For electronic submission, contact DCM at (301) 827-6201.

Copies of the Warning Letters may also be sent to an appropriate state agency. Refer to the Regulatory Procedures Manual, Chapter 4, Advisory Actions, for guidance on this issue.

TABLE OF CONTENTS

PART I - BACKGROUND

Source Plasma, Source Leukocytes, and Therapeutic Exchange Plasma are subject to the licensure provisions of Section 351 of the Public Health Service Act (PHS).

Under the provisions of Section 351 and the Federal Food, Drug, and Cosmetic Act (FD&C), FDA investigators conduct inspections of blood establishments, including those that manufacture or participate in the manufacture of Source Plasma, Source Leukocytes, and Therapeutic Exchange Plasma for human use. The inspection is to ensure that firms manufacture biological products that are safe, pure, potent and have the quality that they represent and that they manufacture these products according to Current Good Manufacturing Practice (CGMP) for Blood and Blood Components regulations and applicable standards. Source Plasma, Source Leukocytes and Therapeutic Exchange Plasma intended for further manufacture into injectable and non-injectable products are biological products. Under the FD&C Act, Source Plasma may have the legal identity of either a drug or a device depending on its intended use. Sources Plasma is subject to the full extent of regulations pursuant to all provisions of the FD&C Act.

FDA began the inspection of Source Plasma establishments in 1973. To provide more effective and efficient regulation of biological products, FDA established Team Biologics in 1997 to conduct routine and compliance follow up CGMP inspections of biological product manufacturers. As part of this program, a cadre of trained investigators has been responsible for inspecting blood banks, Source Plasma establishments and firms associated with those operations. This specialized cadre has proved very effective in performing inspections since 1997 under the Team Biologics Program. Office of Regulatory Affairs (ORA) oversight responsibility for blood and Source Plasma is assigned to the Biological Products Field Committee.

This compliance program builds upon the knowledge gained during previous FDA inspections of the Source Plasma industry and recent scientific developments. It provides a risk-based approach to the GMP inspection of Source Plasma establishments with focus on the operating systems of those establishments.

PART II - IMPLEMENTATION

A. Objective

This program represents a continuing compliance and surveillance activity that began in 1973. The objective of this program is to ensure that Source Plasma, Source Leukocytes, and Therapeutic Exchange Plasma (TEP) for further manufacture into products for human use are safe, effective, appropriately labeled, and have the quality these products are represented to possess. FDA compliance and surveillance activities also assess donor protection provisions to ensure a constant and healthy donor population.

For specific guidance pertaining to the manufacture and inspection of TEP and Source Leukocytes, refer to Attachment K.

The inspection guidance throughout the remaining document applies to the manufacture of Source Plasma. A Source Plasma manufacturing process must:

- Meet the standards described in applicable provisions of the regulations, including those specifically intended to protect donors. These standards include regulations in 21 CFR Parts 600, 601, 606, 607, 610, 630, and 640, process and production controls, equipment regulations and quality assurance in 21 CFR Part 211, and other applicable standards; and
- Meet any additional conditions of licensure included in the Source Plasma manufacturer's approved Biologic License Application.

B. Strategy

This compliance program uses a systems-based approach to conducting an inspection. It identifies 5 systems in the Source Plasma establishment's operation for inspection. The inspection is a comprehensive evaluation of the critical areas in each system. Problems in the critical areas may adversely compromise a Source Plasma donor's safety and/or affect product quality if procedures are not performed properly or system controls are inadequate or function incorrectly. Inspect the following systems:

1. Quality Assurance System – various planned activities that provide confidence that all procedures/processes that influence product manufacture and overall quality are monitored to ensure they are working as expected.
2. Donor Eligibility System – the system that protects the donor's safety, determines donor eligibility for blood collection (including donor deferral resulting from either medical history screening and/or testing), and notifies the donor of ineligibility for donation.
3. Product Testing System – the system that includes procedures to properly test products collected for further manufacture for evidence of communicable disease agents consistent with 21 CFR 610.40.
4. Product Collection and Processing System – the system that controls the collection and processing of Source Plasma, including issues of product quality and donor safety.
5. Quarantine/Storage/Disposition System - the system that manages product quarantine, storage, and distribution (release for use or destruction).

The inspection is based on a multi-layered set of safeguards (referred to as the "five layers of safety") related to the collection, manufacture, and distribution of blood and blood components, including Source Plasma. The five layers of safety are:

1. Donor Screening – procedures to identify donors who have one or more defined risk factors for one or more communicable diseases or who are otherwise ineligible to donate.
2. Donor Deferral – procedures to identify ineligible donors and prevent the distribution of blood products collected from these donors unless the donors participate in a special collection program.
3. Product Testing – procedures to properly test products for further manufacture for evidence of infection by specific communicable disease agents.
4. Quarantining – procedures to ensure that blood products are quarantined until all tests and control procedures are acceptable and unsuitable products are removed from inventory and destroyed or appropriately labeled and distributed; e.g., for use in research, test kit controls, etc.
5. Monitoring and Investigating Problems – procedures to identify system problems, biologic product deviations, and donor adverse reactions, including assurance that adequate corrective action is implemented.

Table 1 – Relationship of Layers of Safety to Source Plasma Systems

Layer of Safety	System(s)
Donor Screening	Donor Eligibility, Quality Assurance
Donor Deferral	Donor Eligibility, Quality Assurance
Product Testing	Product Testing, Quality Assurance, Product Collection and Processing System
Quarantining	Quarantine/Storage/Disposition, Quality Assurance, Product Collection and Processing System
Monitoring and Investigating Problems	Quality Assurance, Product Collection and Processing System

C. Program Management Instructions

This program covers the following establishment types. See Attachment J for definitions and registration requirements.

1. Contractors
2. Off-site Storage Facilities
3. Other Blood Establishments
4. Plasma Brokers
5. Source Plasma Establishments
6. Testing Laboratories

See Attachment K for the manufacture of Source Leukocytes and Therapeutic Exchange Plasma.

Investigators may query the CBER Blood Establishment Registration database on the CBER Intranet, regulatory site to review registration information. The public may access the database through the Internet at http://www.fda.gov/cber/blood/bldreg.htm.

D. Frequency of CGMP Inspections

CGMP inspections are statutory obligations that are routinely conducted on a biennial schedule (based on the previous date of inspection).

The following are exceptions:

1. Firms under a Consent Decree of Permanent Injunction.
2. A new Source Plasma establishment or an establishment re-opening under an existing license is inspected within the first year of operation.
3. A for-cause inspection or a compliance follow-up inspection to verify a Source Plasma establishment's implementation of corrective action after regulatory action.
4. A facility that does not engage in manufacturing, e.g., an off-site storage facility or carrier is inspected at the district's discretion or for cause.
5. A change in location is inspected within 60-90 days of the change or according to district work plans.
6. A Pre-License (PLI) or Pre-Approval inspection (PAI).*
7. A firm or establishment location under a Notice of Intent to Revoke and/or other administrative action.

* Note: The Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs (ORA) jointly conduct PLI inspections with CBER as the lead. Either CBER or ORA may conduct a PAI inspection. PLI and PAI inspections are part of the review of a biologics license application or supplement. CBER identifies the scope and content of the inspection.

E. Scheduling Inspections

ORA and CBER jointly develop the annual inspection workplan**.** District Office staff schedule statutory CGMP inspections of domestic establishments according to the ORA workplan.

Currently, no foreign firm is licensed to manufacture Source Plasma.

For the process that CBER uses to schedule pre-approval and pre-license inspections, refer to Part III, Inspection, Biologic License Applications.

F. Assignment of Investigators and Compliance Personnel

Whenever possible, only Investigators who completed the required Blood Banking and Plasmapheresis training course(s) should inspect establishments covered under this program.

Whenever possible, only Compliance Officers who completed the required Blood Banking and Plasmapheresis training course(s) should process compliance recommendations.

PART III - INSPECTION

A. Strategy

Each inspection of a Source Plasma establishment should extend to the required operating procedures, personnel/training, facilities, equipment, and records of each system. The inspection should include actual observation of the processes applicable to the system.

Inspect each system to the extent necessary to determine whether the Source Plasma manufacturer complies with applicable regulations. The systems for coverage are Quality Assurance, Donor Eligibility, Product Testing, Product Collection and Processing, and Quarantine/Storage/Disposition.

The inspection should cover the following areas of each system:

1. Standard Operating Procedures (SOPs)

   The Source Plasma establishment shall maintain written SOPs that include all steps to be followed in the collection, processing, labeling, storage and distribution of Source Plasma products. SOPs shall be available to personnel in the areas where they perform such operations. [21 CFR 606.100]

2. Training and Personnel

   The personnel responsible for the collection, processing, storage, or distribution of Source Plasma shall be adequate in number, educational background, training and experience, including professional training as necessary, or a combination thereof, to ensure competent performance of assigned functions and to ensure that the final product has the safety, purity, potency, identity, and effectiveness it purports or is represented to possess. [21 CFR 606.20]

   A qualified licensed physician must be on the premises when donor eligibility is determined, immunizations are performed, whole blood is collected, or red blood cells are returned to the donor. [21 CFR 640.62] Most Source Plasma establishments have an approved Physician Substitute (PS**)** training program that allows Source Plasma establishments to train personnel to perform some of the duties of a physician. Each approved program defines the PS's duties. A physician or PS is not required to be physically on the premises, provided the Source Plasma establishment has a procedure that provides medical intervention for a donor within 15 minutes (expeditiously). The physician, however, must be on the premises when the establishment immunizes donors with red blood cells. [21 CFR 640.66]

   If the Source Plasma establishment utilizes a PS, verify that the establishment has an approved PS program CBER may approve a PS training program as an alternative procedure under 21 CFR 640.120.

   The PS should be trained for the functions performed at each location where the PS performs such duties. Note: A Source Plasma establishment may have more than one

individual trained as a PS, and an individual may function as a PS in more than one establishment.

3. Facilities

   Facilities shall be maintained in a clean and orderly manner and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operation. The facility must comply with the requirements of 21 CFR 606.40.
   Conduct a walk-through of the facility to ensure that the facility complies with applicable regulations and to determine if any problem areas exist.

4. Equipment

   Equipment used in the collection, processing, storage, and distribution of Source Plasma, Therapeutic Exchange Plasma and Source Leukocytes shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the SOPs manual. The equipment shall also perform in the manner for which it was designed so as to ensure compliance with the official requirements for Source Plasma manufacture. [21 CFR 606.60]

5. Records

   The Source Plasma establishment must maintain records concurrently with the performance of each significant step in collecting, processing, quarantining, storing, and distributing each Source Plasma product so that all steps can be clearly traced. All records shall be legible and indelible and shall identify the person performing the work, including dates of the various entries, test results as well as interpretation of the result; the expiration date assigned to the specific product; and shall be as detailed as necessary to provide a complete history of the work performed. [21 CFR 606.160]
   Each donor must have a separate and complete record that is cross-referenced to the Source Plasma units collected from the donor. [21 CFR 640.72]

During the inspection,
1. Verify that the Source Plasma establishment maintains all required records applicable to Source Plasma manufacture under 21 CFR 606.160 and the additional records as required under 21 CFR 640.72. All required records must also meet the requirements of 21 CFR 606.160 (a)(1) and (2). 2. Review as many records as necessary in each system to verify that records are complete and maintained as required and that each record contains positive identification of the donor on all records describing the history and disposition of Source Plasma products. [21 CFR 640.64, 640.65, 640.72]

B. Plasma Brokers

Inspecting a Plasma Broker is required only if the broker takes possession of Source Plasma products and performs a manufacturing operation; e.g., culling out unsuitable Source Plasma units.

During the inspection,
At a minimum, evaluate the broker's compliance with the following regulations: 21 CFR 606.100(b)(10), 606.160(b)(2) and (3), 606.165, 607, and 640.70. These regulations pertain to storage, records of product receipt, product pooling, labeling, distribution and registration.

C. Contractors

A Source Plasma manufacturer may contract with another establishment to perform one or more manufacturing steps. Both the Source Plasma manufacturer and contractor are responsible for product quality. The Source Plasma establishment, as the license holder, remains responsible for compliance with applicable product and establishment standards. The contractor is responsible for complying with applicable CGMP. Inspect contractors that perform services, such as testing, pooling, culling, and/or preparing and supplying Red Blood Cell immunogen cells to a Source Plasma manufacturer.
http://www.fda.gov/cber/gdlns/coopmfr.pdf

During the inspection,
1. Determine the extent of services provided. 2. Determine each party's responsibility for the product or operations performed. 3. Determine who prepared the SOPs used by the contractor. 4. Determine who performed product quality control tests

D. Biologic License Applications (BLAs)

FDA licenses Source Plasma, a biological product, under the authority of section 351(a) of the PHS Act. A biologics license must be in effect for a biological product prior to its introduction or delivery for introduction into interstate commerce.

CBER issues a single BLA tracking number to an applicant (the person or legal entity who submits an application to manufacture a product subject to licensure). The applicant may submit separate supplements to the BLA to manufacture individual products. CBER approves a BLA to manufacture Source Plasma and issues a U.S. license number to the applicant if the applicant can manufacture Source Plasma products that are safe, pure, potent and effective for their intended use and maintains an establishment to manufacture Source Plasma that meets CGMP and other standards designed to ensure that Source Plasma products remain safe, pure, potent and effective for their intended use. [21 CFR 601.4] The U.S. license number must appear on the product label.

Prior to issuing a biologics license, a pre-license inspection (PLI) is conducted by a CBER product specialist and, whenever possible, a district investigator, to determine if the Source

Plasma establishment is able to comply with applicable regulations for manufacture. CBER notifies ORA/Division of Field Investigations or appropriate district office in advance of a scheduled PLI. CBER has the lead in these inspections.

Licensed manufacturers must submit a written request, as appropriate, to CBER to implement a change in a licensed product, a production process, quality control, equipment, or to a facility previously approved in a license application. [See 21 CFR 601.12 and the Guidance for Industry, "Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture." http://www.fda.gov/cber/gdlns/bldchanges.htm]

E. Inspection Guidance

Inspection guidance for coverage of the critical areas of each of the 5 systems for inspection and other relevant inspection issues are included in the following attachments:

1. Attachment A - Quality Assurance System (QA)
2. Attachment B - Donor Eligibility System
3. Attachment C - Product Testing System
4. Attachment D - Quarantine/Storage/ Disposition System
5. Attachment E - Product Collection and Processing System
6. Attachment F - Computers
7. Attachment G - Lookback
8. Attachment H - Physician Substitutes
9. Attachment I - Source Plasma Collection Programs
10. Attachment J - Types of Blood Establishments
11. Attachment K - Source Leukocytes and Therapeutic Exchange Plasma

PART IV - ANALYTICAL

A. Analyzing Laboratories

No field analyses are planned under this program.

When analyses are required, refer to the following chart for guidance.

Individual	**Responsibility**
Sample Custodian	Arranges for the testing of any physical sample collected on an assignment
	Receives samples Ensures staff availability for sample arrival
	Address: Sample Custodian (Attention: HFM-672) Center for Biologics Evaluation and Research Bldg. B., Room 113 5516 Nicholson Lane Kensington, MD 20895 **Telephone:** 301-594-6517 **FAX:** 301-594-6924
HFM-650	Returns test results to the Director, Division of Inspections and Surveillance
	Provides contact(s) to respond to questions regarding analytical results **Telephone:** 301-827-6220
Investigator	Obtains packaging and shipping information from Sample Custodian
	Prior to shipment, notifies the Sample Custodian of projected date of sample arrival
	Sends test samples to the Sample Custodian by courier

PART V - REGULATORY/ADMINISTRATIVE STRATEGY

When inspection findings demonstrate that a manufacturer of Source Plasma is not operating in a state of control and/or the establishment's management is either unwilling or unable to implement adequate corrections in a timely manner, districts should consider the advisory, administrative and/or judicial options currently available. A firm is considered to be operating in a state-of-control when it employs conditions and practices that ensure compliance with the intent of Section 501(a)(2)(B) of the FD&C Act, and the portions of the CGMP regulations that pertain to its systems. A firm in a state of control produces products for which there is an adequate level of assurance of quality, identity, purity and potency.

The District Office should base all regulatory recommendations on significant deviations that are well documented. The quality of any action begins with the quality of evidence collected at the time of the inspection to support the observed objectionable conditions. The recognition, collection, and effective presentation of evidence are essential to successful judicial, regulatory, or administrative actions. The identification of those responsible for violations is also a critical part of the inspection. Establish responsibility and identify persons to hold accountable for violations, and with whom the Agency must communicate to seek lasting corrections and/or to be the subject of enforcement actions. The decision on the type of action to recommend should be based on the seriousness of the documented deficiencies with regard to, and the most effective way to protect, public health.

A firm's written corrective action, in response to the FDA-483, should not preclude the consideration of an advisory, administrative, or judicial action. Recommend such action, if the objectionable observations represent (a) a continuing pattern of non-compliance, (b) a failure to correct significant deficiencies noted during a previous inspection, or (c) the deficiencies pose a significant threat to the public health, and voluntary action is either not appropriate or can not be readily accomplished.

For products intended for further manufacture, the advisory, administrative, and judicial options available include:

Action	**Among other things, consider if,**
Warning Letter	Violations of regulatory significance that causes one or more systems to be considered not in a state of control.
License Revocation 21 CFR 601.5	Notice of Intent to Revoke with Opportunity for Correction: • Unable to gain access to the manufacturing facility for inspection. • Licensed products are not safe or effective for their intended use, or are misbranded with respect to any such use. • Manufacturer fails to report a major change in manufacture. • Manufacturer fails to conform to applicable standards to ensure product safety, potency, and purity.

Action	Among other things, consider if,
	• Licensed products are no longer manufactured. Direct Revocation without Opportunity for Correction • Demonstration of willful disregard.
License Suspension 21 CFR 601.6	Summary action taken by the Agency and may be an intermediate step in the revocation process. Reasonable grounds for revocation and a danger to health exist. It provides immediate withdrawal of the authorization to ship a biological product in interstate commerce.
Seizure	Manufacturer is unwilling or unable to retrieve violative products or products held for sale are unsuitable for safe use. U.S. Marshal takes possession of products through Court Order pursuant to Section 304 of the FD&C Act.
Injunction	Civil process initiated to stop or prevent violation of the law; i.e., to halt the flow of violative products in interstate commerce and to correct the conditions that caused the violation to occur. Action taken when a current health hazard exists, the establishment has a history of uncorrected deviations despite previous warnings, suspension of the firm's license would result in an unacceptable shortage of products, and/or to halt intrastate distribution of products manufactured under violative conditions.
Prosecution	Fraud, gross, flagrant, or intentional violations, health hazards, or serious, continuing, or uncorrected violations.

Districts should initially consider an advisory action, such as a warning letter, if there is no previous violative history at the firm.

To determine the appropriate action, consult with CBER/Office of Compliance and Biologics Quality (OCBQ)/Division of Case Management (HFM-610), early in the investigation, and consult the Regulatory Procedures Manual (RPM). This early consultation is especially critical when immediate action is indicated (e.g., license suspension or temporary restraining order (TRO)). See RPM Chapter 6, regarding TROs and an injunction to protect the public health. When inspection findings indicate the potential for fraud (e.g., falsification, counterfeiting, illegal importation, drug diversion), the investigator should notify his/her supervisor, who will notify CBER/OCBQ. District management will alert the appropriate Office of Criminal Investigations Office, as appropriate. The investigator should, however, continue to pursue any public health concerns, in coordination with CBER/OCBQ, concurrently.

Evidence of significant and /or a pattern of deficiencies (history) within a system covered could constitute failure of the system. **The District should classify as Official Action Indicated, an inspection report that documents one or more systems as not in a state of control.** The District should then consider a Warning Letter or other appropriate action. When deciding the type of action to recommend, follow the RPM and base the initial decision on the seriousness and /or frequency of the problem and the firm's compliance history.

Districts may issue Warning Letters per RPM Chapter 4, to warn establishments of violations, to solicit voluntary corrections, and to provide for the initial phase of formal Agency regulatory action. The RPM outlines the types of letters requiring CBER concurrence prior to issuance. All Warning and Untitled Letter recommendations require Office of Chief Counsel review and clearance.

A. Deficiencies

The following, although not all-inclusive, are examples of deficiencies that may be indicative of the firm's state-of-control:

1. General

    a. Any practice or pattern of practices that poses a danger to public health and warrants grounds for license revocation [21 CFR 601.6 (a)]
    b. Failure to provide adequate facilities and to maintain them in a clean and orderly manner [21 CFR 606.40]
    c. Failure of a licensed establishment to notify CBER of any change that has a substantial potential to have an adverse effect on the product as it relates to the safety or effectiveness of the product [21 CFR 601.12(b)]
    d. Falsifying, changing or altering product labels or records [42 U.S.C. 262(b) 21 CFR 606.160; 640.70; 640.72]
    e. A history of similar significant deficiencies
    f. Recurrent problems with a computer system(s), such as a donor deferral system, testing equipment interface, labeling system, and/or quarantine/distribution system that could lead to the release of unsuitable products [21 CFR 211.68(b)]
    g. Any failure to completely identify the container or laboratory samples so they can be correlated to the individual donor [21 CFR 606.140(c); 606.160(c); 640.72(a)(2)]
    h. Failure of the physician to be physically on premises during red blood cell immunizations [21 CFR 640.62]

2. Quality Assurance System

    a. Failure to establish and implement a written quality assurance program [21 CFR 211.22(d), 211.100, and 606] (Reference this item when substantive deficiencies are noted that lead to a conclusion that system and process controls are inadequate and cannot prevent violative conditions.)
    b. Lack of computer and/or software validation or a lack of documentation associated with the performance or analysis of validation activities [21 CFR 606.160; 211.68(b)]
    c. Failure to establish and implement adequate computer security provisions (passwords, user, ID's, and modem access) to ensure data integrity [21 CFR 211.68(b)]
    d. Personnel inadequately trained or supervised in the operations they perform to such an extent that a danger to the health of the donor or safety of the product exists [21 CFR 606.20 and 640.64(a)]
    e. A physician substitute supervising an immunization program prior to receiving appropriate training and / or an individual performing the duties of a physician substitute prior to CBER approval of a Source Plasma establishment's physician substitute training program [21 CFR 606.20(b) and 640.66]
    f. A pattern of personnel training deficiencies [21 CFR 606.20]
    g. Failure to maintain, standardize, calibrate, and follow established procedures for

equipment used in the collection, processing, testing, storage, and distribution of Source Plasma [21 CFR 606.60]

h. Failure to recognize, adequately respond to, and investigate adverse reactions and document and maintain appropriate records [21 CFR 606.170(a) and 606.100(b)(9)]
i. Duplicate, discrepant, or invalid records existing in the computer's donor deferral files that could lead to the acceptance of unsuitable donors and release of unsuitable products. [21 CFR 606.160(b), 606.100(c) and 211.68]
j. Failure to immunize donors by acceptable procedure(s) and/or use approved antigens [21 CFR 640.66]
k. Failure to advise CBER of fatalities resulting from complications related to blood collection and failure to investigate the cause of death [21 CFR 606.170(b)]
l. Failure to thoroughly investigate and incorporate appropriate corrections concerning any unexplained discrepancy or the failure of a lot or a unit to meet specifications that may affect the safety, purity, or potency of the product [21 CFR 606.100(c)]
m. Failure to promptly notify CBER of biological product deviations in the manufacture of Source Plasma that may affect the safety, purity, or potency of the product [21 CFR 606.171(c) and (e)]
n. Use of unapproved procedures pertaining to major changes and/or implementation of unapproved major changes in manufacturing methods. [21 CFR 601.12]
o. Failure to establish procedures and/or repeated failure to follow SOPs and/or to maintain appropriate records for the proper handling of post donation information reports (CPG 230.140) [21 CFR 211.100, 211.192; 211.198; 606.100; and 606.160]
p. Failure to establish written procedures and maintain adequate records for an immunization program [21CFR 606.160(a)(1); 640.66; CPG 250.100]

3. Donor Eligibility System

a. Failure to establish a donor identification system that confirms donor identity and correlates medical records, test results, and components to the donor record [21CFR 640.65(b)(3); 640.72(a)(2)]
b. Any personnel or system failure that causes the establishment to accept or inappropriately re-enter ineligible donors [21 CFR 606.20(b), 640.63(a), and 640.640]
c. Failure to establish or repeated failure to follow SOPs for donor eligibility determinations [21 CFR 606.100(b)(1) and (2); 640.63]
d. Failure to explain hazards or risks of procedure by a physician or designee, to obtain a signed informed consent form, or implement appropriate safeguards to minimize the potential for transmission of unexpected infectious agents [21 CFR 606.160(b)(1)(v), 606.100(b), 640.61 and CPG 250.100]
e. Failure to properly determine the eligibility of the donor (e.g., routine physical examinations, medical history questions, hemoglobin, blood pressure, temperature, or total protein) [21 CFR. 640.63, 640.65(b)(2)(i), and 606.20(b)]
f. Failure to perform and adequately document physician’s review of laboratory and collection records [21 CFR 640.65(b)(2)]
g. Failure to have a licensed physician perform physical examinations for immunization, unless approved as an alternative procedure under 21 CFR 640.120 [21 CFR 640.63 (b)(2)(i)]
h. Failure to maintain accurate records that identify ineligible donors so that the establishment will not distribute products from such individuals [21 CFR 606.160 (b)(1) and (e)]
i. Pattern of failure to make a reasonable attempt to notify donors of deferral status

[21 CFR 630.6]

4. Product Testing System

   a. Any failure to perform viral marker testing or a serological test for syphilis [21 CFR 610.40 and 640.65 and 640.67]
   b. Failure to perform tests or interpret results according to manufacturers' instructions and specifications; e.g., use of outdated reagents or mixing of reagents from different master lots; failure to run the proper number of controls concurrently with the test; inappropriate invalidation of test results; calculations incorrectly determined resulting in reactive results being interpreted as nonreactive; interpreting reactive test results as nonreactive; and failure to conduct necessary retests. [21CFR 610.40, and 606.65(e)]
   c. Viral marker tests not performed using an approved or licensed test kit or otherwise allowed in 21 CFR 610.40.
   d. Incomplete or inaccurate testing records, including all records associated with invalidated test runs [21 CFR 606.160(b)(2)(i); 640.72(a)(2)]

5. Quarantine / Storage / Disposition System

   a. Source Plasma and/or other products for further manufacture not stored at proper temperature [21 CFR 610.53, 640.69(b), 640.74]
   b. Failure to maintain temperature records when Source Plasma is in storage or shipped. [21 CFR 606.160(b)(3)(iii); 640.72(a)(1)]
   c. Failure to store final containers under conditions that prevent exposure of the product to external factors that may cause deterioration or contamination [21 CFR 640.68(b)]
   d. Failure to establish or follow a system that prevents the distribution of any products not suitable for use [21 CFR 606.40(a)(6); 606.40(d)(2); 606.100(b); 606.160(e); and 610.40 (h)]
   e. Failure to obtain CBER approval to ship product that is not tested for communicable disease agents required in 21 CFR 610.40.
   f. Failure to establish or follow a system by which receipt and distribution of each unit of Source Plasma can be readily determined to facilitate recall, if necessary [21 CFR 606.165(a)]
   g. Failure to quarantine unsuitable products or to notify consignees in accordance with 21 CFR 610.46(a)

6. Product Collection and Processing System

   a. Failure to collect Source Plasma by methods that protect against contamination of the final product and returned red blood cells [21 CFR 640.64(b) and (e)]
   b. Failure to follow equipment manufacturer’s instructions for plasmapheresis procedures [21 CFR 640.65, 606.60]
   c. Failure to use approved containers for the collection of Source Plasma [21 CFR 640.68(b)]
   d. Failure to maintain complete and accurate processing records [21 CFR 606.160(a)(1), (b)(2); 640.72]
   e. Failure to properly label blood components [21 CFR 610.62 and 640.70]
   f. Failure to record whole blood weights in manual collection and to recognize and/or correct overbleeding in manual or automated collection procedures [21 CFR 640.65(b)(4)(5)(6) and (8) and 606.160(a)(1) and CPG 252.100]
   g. Failure to prevent the infusion of one donor’s red blood cells into another donor [21

CFR 640.65(b)(3) and 606.100(b)(17)]

B. Federal / State Relations

Currently FDA has no formal cooperative program with state or local jurisdictions to inspect or regulate Source Plasma establishments. Nonetheless, districts should cooperate with these authorities, especially if the state or local jurisdiction has a regulatory program. Whenever possible, districts should exchange information with all levels of government consistent with information disclosure procedures. Provide a copy of a warning letter to the appropriate state agency or agencies. If a state official requests a copy of the Form FDA-483, redact the document according to FOI procedures prior to release. For additional assistance, contact the Office of Regulatory Affairs/Division of Federal State Relations (HFC-150) at (301) 827-6906.

PART VI REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

A. Laws And Regulations

1. Federal Food, Drug, and Cosmetic Act as Amended and Related Laws.
   http://www.fda.gov/opacom/laws/fdcact/fdctoc.htm

2. Public Health Service Act, Subpart I - Biological Products.
   http://www.fda.gov/opacom/laws/phsvcact/phsvcact.htm

3. Title 21, Code of Federal Regulations, Parts 211, 600, 601, 606, 607, 610, 640 and 820.
   http://www.gpoaccess.gov/cfr/index.html

B. ORA Inspection Manuals and Inspection Guides

1. FDA Investigations Operations Manual, 2004 or latest edition. Sections 500-529, 560-565, 590-595, 635, 773, 921, 924, 927-928, 1026 and Appendix B.
   http://www.fda.gov/ora/inspect_ref/iom/

2. FDA Regulatory Procedures Manual (RPM), March 2004 or latest edition. Chapter 4 – Advisory Actions, Chapter 5- Administrative Actions, Chapter 6 – Judicial Actions, Chapter 7 – Recall and Emergency Procedures, Chapter 9 – Import Operations/Actions.
   http://www.fda.gov/ora/compliance_ref/rpm/

3. FDA Office of Regulatory Affairs Warning Letter Reference Guide, October 1994.

4. FDA Compliance Policy Guides, August 2000 or latest edition, Chapter 1 - General and Chapter 2 – Biologics.
   http://www.fda.gov/ora/compliance_ref/cpg/default.htm

5. Guide to Inspections of Infectious Disease Marker Testing Facilities, June 1996.
   http://www.fda.gov/ora/inspect_ref/igs/infdis.html

6. Guide to Inspection of Source Plasma Establishments, June 1997 (April 2001 - Editorial Revisions)
   http://www.fda.gov/ora/inspect_ref/igs/Source_Plasma/default.htm

C. Guidance Documents and Memoranda Pertaining to Source Plasma Manufacture

1. Donor (Suitability) Eligibility

   a. Guidance for Industry: Revised Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection, May 1, 2003.
      http://www.fda.gov/cber/gdlns/wnvguid.pdf

   b. Guidance for Industry: Recommendations for the Assessment of Donor Suitability and Blood Product Safety in Cases of Suspected Severe Acute Respiratory Syndrome

(SARS) or Exposure to SARS, April 2003.
http://www.fda.gov/cber/gdlns/sarsbldgd.htm

c. Question and Answer on FDA Guidance Entitled "Recommendations for The Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Suspected and Probable Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS," June 5, 2003.
http://www.fda.gov/cber/gdlns/sarsbldq&a.htm

d. Guidance for Industry: Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients, December 30, 2002.
http://www.fda.gov/cber/gdlns/smpoxdefquar.htm

e. Questions and Answers on FDA Guidance Entitled "Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients,"
http://www.fda.gov/cber/gdlns/smpoxdefquarq&a.htm

f. Guidance for Industry: Recommendations for Assessment of Donor Suitability and Blood Product Safety in Cases of Possible Exposure to Anthrax, October 17, 2001.
http://www.fda.gov/cber/gdlns/anthraxexp.htm

g. Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products, January 2002.
http://www.fda.gov/cber/gdlns/cjdvcjd.htm

h. Interim Recommendations for Deferral of Donors at Increased Risk for HIV-1 Group O Infection, December 11, 1996.
http://www.fda.gov/cber/bldmem/mem121196a.txt

i. Donor Deferral Due to Red Blood Cell Loss During Collection of Source Plasma by Automated Plasmapheresis, December 4, 1995.
http://www.fda.gov/cber/bldmem/mem120495.pdf

j. Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma, June 8, 1995.
http://www.fda.gov/cber/bldmem/060895.txt

k. Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis, December 22, 1993.
http://www.fda.gov/cber/bldmem/122293.txt

l. Deferral of Blood and Plasma Donors Based on Medications, July 28, 1993.
http://www.fda.gov/cber/bldmem/072893.txt

m. Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products, April 23, 1992.
http://www.fda.gov/cber/bldmem/hiv042392.pdf

n. Exemptions to Permit Persons with a History of Viral Hepatitis Before the Age of Eleven Years to Serve as Donors of Whole Blood and Plasma: Alternative Procedures, 21 CFR 640.120 April 23, 1992.
http://www.fda.gov/cber/bldmem/042392ex.txt

o. Deferral of Donors Who Have Received Human Pituitary-Derived Growth Hormone, November 25, 1987.
http://www.fda.gov/cber/bldmem/112587.txt

2. Source Plasma Collection and Special Programs

a. Guidance for Industry: CBER Pilot Licensing Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained From An Outside Supplier, July 11, 2001
http://www.fda.gov/cber/gdlns/immrbcs.htm

b. Donor Deferral Due to Red Blood Cell Loss During Collection of Source Plasma by Automated Plasmapheresis, December 4, 1995.
http://www.fda.gov/cber/bldmem/mem120495.pdf

c. CBER Draft Reviewers' Guide for Disease Associated Antibody Collection Program, October 1995.
http://www.gov/cber/gdlns/antbdyclcprgm.pdf

d. Draft Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires, April 19, 2002.
http://www.fda.gov/cber/gdlns/donorsaq.htm

e. Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors, March 14, 1995.
http://www.fda.gov/cber/bldmem/031495.txt

f. Revision of FDA Memorandum of August 27, 1982: Requirements for Infrequent Plasmapheresis Donors, March 10, 1995.
http://www.fda.gov/cber/bldmem/031095.txt

g. Volume Limits for Automated Collection of Source Plasma, November 4, 1992.
http://www.fda.gov/cber/bldmem/110492.txt

h. Revisions to 26 October 1989 Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors), April 17, 1991.
http://www.fda.gov/cber/bldmem/041791.txt

i. Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors), October 26, 1989.
http://www.fda.gov/cber/bldmem/102689.txt

j. Extension of Dating Period for Storage of Red Blood Cells, Frozen, December 4, 1984.
http://www.fda.gov/cber/bldmem/120487.txt

k. Plasma Derived from Therapeutic Plasma Exchange, December 14, 1984.
http://www.fda.gov/cber/bldmem/121484.txt

l. Guidelines for the Collection of Human Leukocytes for Further Manufacturing (Source Leukocytes), January 28, 1981.
http://www.fda.gov/cber/bldmem/012881.pdf

m. Guidelines for Immunization of Source Plasma (Human) Donors with Blood Substances, June 1980.
http://www.fda.gov/cber/gdlns/imnztnsrcpl.pdf

3. Infectious Diseases

a. Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV, October 21, 2004.
http://www.fda.gov/cber/gdlns/hivhcvnatbld.htm

b. Draft Guidance for Industry: Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis - 6/25/2003
http://www.fda.gov/cber/gdlns/syphilis.pdf

c. Draft Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts, February 1, 2002.
http://www.fda.gov/cber/gdlns/zoobldxeno.pdf

d. Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products, January 9, 2002.
http://www.fda.gov/cber/gdlns/cjdvcjd.htm

e. Questions and Answers on FDA Guidance Entitled Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob (CJD) Disease and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products. Last updated 1/22/04.
http://www.fda.gov/cber/gdlns/cjdvcjdq&a.htm

f. Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV, December 4, 2001. (For comment only)

g. Draft Guidance for Industry: Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma, November 26, 1999.
http://www.fda.gov/cber/gdlns/ppnat.htm

h. Draft Guidance for Industry: Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis C Virus (HCV); (2) Supplemental Testing and the Notification of Consignees and Transfusion Recipients of donor Test Results for Antibody to HCV (Anti-HCV), June 17, 1999. (For comment purposes only).
http://www.fda.gov/cber/gdlns/hcvlkbk.htm

i. Guidance for Industry: Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for antibody to Hepatitis C Virus (Anti-HCV); (2) Supplemental Testing and the Notification of Consignees and Blood Recipients of Donor Test Results for Anti-HCV, September 23, 1998. Obtain (Doc 0621) from CBER/OCTMA/HFM-40, 1401 Rockville Pike, Rockville, MD 20852 1-800-835-4709.

j. Interim Recommendations for Deferral of Donors at Increased Risk for HIV -1 Group O Infection, December 11, 1996.
http://www.fda.gov/cber/bldmem/mem121196a.txt

k. Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human T- Lymphotropic Virus Type I (HTLV-I), July 19, 1996. Note: The HCV section of this document is superseded by guidance document dated September 23, 1998.
http://www.fda.gov/cber/bldmem/mem71996.txt

l. Additional Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), May 16, 1996.
http://www.fda.gov/cber/bldmem/antigen1.txt

m. Additional Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen, March 14, 1996
http://www.fda.gov/cber/bldmem/antigen1.txt

n. Recommendation for Donor Screening with a Licensed Test for HIV-1 Antigen, August 8, 1995
http://www.fda.gov/cber/bldmem/hiv-ag.txt

o. Recommendations to Users of Medical Devices that Test for Infectious Disease Markers by Enzyme Immunoassay (EIA) Test Systems, December 20, 1994.
http://www.fda.gov/cber/bldmem/122094.txt

p. Clarification of the Use of Unlicensed Anti-HCV Supplemental Test Results in Regard to Donor Notification, August 19, 1993.
http://www.fda.gov/cber/bldmem/081993.txt

q. Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), August 5, 1993.

http://www.fda.gov/cber/bldmem/080593.txt

r. Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products, April 23, 1992. http://www.fda.gov/cber/bldmem/hiv042392.pdf

s. Use of Fluorognost HIV-1 Immunofluorescent Assay (IFA), April 23, 1992. http://www.fda.gov/cber/bldmem/042392.txt

t. Use of Genetic Systems HIV-2 EIA, June 21, 1990. http://www.fda.gov/cber/bldmem/062190.txt

u. HTLV-1 Antibody Testing (to Licensed Source Plasma Manufacturers Approved for Immunization with Red Blood Cells) July 6, 1989. http://www.fda.gov/cber/bldmem/070689.pdf

v. Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBSAG), December 2, 1987. http://www.fda.gov/cber/bldmem/120287.pdf

4. Inspections

a. Draft Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments, August 10, 2001. http://www.fda.gov/cber/gdlns/devbld.htm

b. Guideline for Quality Assurance in Blood Establishments, July 11, 1995. http://www.fda.gov/cber/gdlns/gde_qa.txt

c. Discontinuance of Pre-License Inspection of Immunization Using Licensed Tetanus Toxoid and Hepatitis B and Rabies Vaccine, July 7, 1988. http://www.fda.gov/cber/bldmen/070788.txt

d. Control of Unsuitable Blood and Blood Components, April 6, 1988. http://www.fda.gov/cber/bldmem/040688.txt

5. Labeling

a. Guidance for Industry: Recognition and Use of a Standard for the Uniform Labeling of Blood and Blood Components, June 6, 2000. http://www.fda.gov/cber/gdlns/unilabbld.htm

b. Guidance for Industry: United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128, November 1999. http://www.fda.gov/cber/gdlns/ISBT128Nov99.pdf

c. Recommendations for Labeling and Use of Units of Whole Blood, Blood Components, Source Plasma, Recovered Plasma or Source Leukocytes Obtained from Donors with Elevated Levels of Alanine Aminotransferase, (ALT), August 8, 1995. http://www.fda.gov/cber/bldmem/alt.txt

d. Guideline for the Uniform Labeling of Blood and Blood Components, August 1985. [Obtain Document D0053 from CBER, OCTMA, HFM-40, 1-800-835-4709 or 301-827-1800.]

6. Miscellaneous

a. Draft Guidance for Industry: Acceptable Full-length Donor History Questionnaire and Accompanying Materials for Use in Screening Human Donors of Blood and Blood Components, April 23, 2004.
http://www.fda.gov/cber/gdlns/donorhistques.pdf

b. Guidance for Industry: Streamlining the Donor Interview Processes: Recommendations for Self-Administered Questionnaires, July 3, 2003.
http://www.fda.gov/cber/gdlns/donorsaq.htm

c. Draft Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, June 3, 2002. (For comment only)
http://www.fda.gov/cber/gdlns/bldfatal.htm

d. Draft Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments, August 10, 2001. (For comment only)
http://www.fda.gov/cber/gdlns/devbld.htm

e. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, August 7, 2001.
http://www.fda.gov/cber/gdlns/bldchanges.htm

f. Guidance for Industry: Revised Recommendations Regarding Invalidation of Test Results of Licensed and 510(k) Cleared Bloodborne Pathogen Assays Used to Test Donors, July 11, 2001.
http://www.fda.gov/cber/gdlns/bldbrn.htm

g. Guidance for Industry CBER Pilot Licensing Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier, July 18, 2000.
http://www.fda.gov/cber/gdlns/immrbcs.htm

h. Options for Alternative Arm Preparation – Clinipad Recall 3/9/2000; (Updated 4/25/2001).
http://www.fda.gov/cber/blood/armpreprev.htm

i. Draft Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics, August 1999.
http://www.fda.gov/cber/gdlns/coopmfr.pdf

j. Guidance for Industry: Errors and Accidents Regarding Saline Dilution of Samples Used for Viral Marker Testing, June 11, 1998.
http://www.fda.gov/cber/gdlns/easaline.htm

k. FDA Guidance for Industry on: Exports and Imports Under the FDA Export Reform and Enhancement Act of 1996, Draft February 1998.
http://www.fda.gov/opacom/fedregister/frexport.html

l. Draft Reviewer's Guide: Informed Consent for Plasmapheresis/Immunization, October 1995.
http://www.fda.gov/cber/gdlns/infrmdcnsntplsm.pdf

m. CBER Draft Reviewers' Guide for Disease Associated Antibody Collection Program, October 1995.
http://www.fda.gov/cber/gdlns/antbdyclcprgm.pdf

n. Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma, March 14, 1995.
http://www.fda.gov/cber/bldmem/031495.txt

o. Guidance Regarding Post Donation Information Reports, December 10, 1993.
http://www.fda.gov/cber/bldmem/121093.txt

p. Physician Substitutes, August 15, 1988.
http://www.fda.gov/cber/bldmem/081588.txt

7. Computers

a. Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application, September 3, 2003.
http://www.fda.gov/cber/gdlns/prt11elect.pdf

b. General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 11, 2002.
http://www.fda.gov/cdrh/comp/guidance/938.html

c. Reviewer Guidance for a Pre-market Notification Submission for Blood Establishment Computer Software, January 13, 1997.
http://www.fda.gov/cber/gdlns/swreview.txt

d. Glossary of Computerized System and Software Development Terminology, August 1995.
http://www.fda.gov/ora/inspect_ref/igs/gloss.html

e. Letter to Blood Establishment Computer Software Manufacturers, March 31, 1994.
http://www.fda.gov/cber/bldmem/033194.txt

f. Recommendation for Implementation of Computerization of Blood Establishments, April 6, 1988.
http://www.fda.gov/cber/bldmem/040688co.txt

g. Guideline on General Principles of Process Validation, May 1987.
http://www.fda.gov/cber/gdlns/validation0587.pdf

h. Guide to Inspection of Computerized Systems in Drug Processing, February 1983 http://www.fda.gov/ora/inspect_ref/igs/csd.html

D. Center for Biologics Evaluation and Research and Office of Regulatory Affairs Program Contacts

1. Office of Compliance and Biologics Quality, HFM-600

Immediate Office of the Director, HFM-600
Anita Richardson, 301-827-6190, FAX 301-827-3391

General Policy Issues

Division of Case Management, HFM-610
Mary Malarkey, Director, 301-827-6201, FAX 301-594-0940

Advertising and Promotional Labeling; Application Integrity; Biological Product Recalls; Certificates of Export; Citations; Civil Money Penalties; Compliance Status Checks; Debarment; Import/Export Programs; Injunctions; License Suspensions; Prosecutions; Revocations and Denials; Seizures; Tissue Recall Orders; Warning Letters

Blood and Tissue Compliance Branch, HFM-614
(Vacant) Branch Chief 301-827-6201, FAX 301594-0940

Thomas Adams	Wendy Hively
Helen Cowley	Stephany Kersten Wesley
Diane Hall	Armando Zamora
Laura Hieronymus	

Division of Inspections and Surveillance, HFM-650
(Vacant) Director 301-827-6220, FAX: 301-827-6748

Program Surveillance Branch, HFM-654
Gilliam Conley, Chief, 301-827-6220

Hang Dinh	
Anthony Hawkins	
Maureen Knippen	
Sharon O'Callaghan	Biological Product Deviations
Susan Cannon	Biological Product Deviations
Lois Simmons	Fatality Program Fatality Transfusion Reporting fatalities2@cber.fda.gov Voice Mail: 301-827-6220 FAX: 301-827-6748
Patricia Y. Jones	Blood and Plasma Programs & Licensing Changes

2. Office of Blood Research and Review, HFM-300

Division of Blood Applications, HFM-370

Alan Williams**,** Director, 301-827-3524, FAX: 301-827-3535

Blood Registration Coordinator
Janet Ishimoto 301-827-3546

Registration, Licensing, Labeling, Variances, Approvals for Changes

Blood and Plasma Branch, HFM-375

Sharyn Orton**,** Branch Chief, 301-827-3543, FAX: 301-827-3534

Linda Alms	Joseph Manik
Karan Blum	Monica Yu
Judy Ciaraldi	Hoi-May Wong
Marla Cohen	Kenneth Zemann

3. Office of Regional Operations

ORO/Division of Field Investigations, HFC-130

Michael C. Rogers, Director DFI, 301-827-5658, FAX 301-827-6685
Mary Carden, National Expert, 716-541-0352
Joan Loreng, National Expert, 215-362-0740, X11
Joyce Watson, CSO (Foreign Inspections), 301-827-5664

ORO/DFI/Biologics Group, HFC-132

Gerald W. Miller, SCSO, 301-827-5655, FAX 301-443-3757
Christine Twohy, CSO, 301-827-5662
Gail Katz, CSO, 301-827-3357

PART VII - CENTER FOR BIOLOGICS EVALUATION AND RESEARCH RESPONSIBILITIES

The Center for Biologics Evaluation and Research (CBER), through its Office of Compliance and Biologics Quality (OCBQ)/Division of Inspections and Surveillance (DIS), works cooperatively with the Office of Regulatory Affairs (ORA) Biological Program Committee to monitor the inspection and compliance accomplishments under this compliance program, and the status of the establishments inspected under this program. The ORA annual workplan, developed by CBER and ORA, provides overall resource allocations and anticipated numbers of inspections. However, current industry practices encountered during an inspection, the past compliance history of an establishment, or other compliance developments, may necessarily result in unplanned inspections or in individual CGMP inspections taking more or less time than estimated in the workplan.

ORA continues to have the primary responsibility for ensuring (1) that the program strategies, priorities, and procedures articulated in this compliance program are followed by the ORA Field staff and (2) that potential problems or needs for policy/program clarification are brought to CBER's attention. CBER and ORA jointly coordinate activities to achieve industry compliance with applicable laws, regulations, and court orders (e.g., Consent Decrees of Permanent Injunction).

CBER/OCBQ will continue to use accomplishment data from the ORA Field Accomplishment and Compliance Tracking System (FACTS), legal or administrative action recommendations, requests for policy decisions/clarification received from the public or the blood industry, and input from CBER scientific and product experts to provide overall direction to FDA's blood safety initiatives that are supported by this risk-based compliance program.

CBER/OCBQ will send to the appropriate district Director of Investigation Branch email attachments containing approved changes to biologic license applications.

The Biological Products Field Committee and the OCBQ Division of Inspections and Surveillance intend to have periodic conference calls concerning this program and an annual meeting, with other ORA and CBER units (e.g., CBER Office of Blood Research and Review) participating as necessary.

CBER/OCBQ will carefully evaluate the experience with this systems-based inspection program through inspection reports and other compliance data to determine its effectiveness and to continually assess and improve the quality of the CBER products inspection program. CBER/OCBQ also will carefully review and monitor industry compliance, product developments within industry, and the safety and quality of Source Plasma.

ATTACHMENT A

QUALITY ASSURANCE SYSTEM

The Source Plasma establishment's quality assurance (QA) program should consists of various planned activities to provide confidence that all procedures/processes that influence Source Plasma manufacture and overall quality of the final product are working as expected. The QA program should include validation of processes. This activity, referred to as process validation, is a controlled system of activities that establishes through documented evidence that the establishment's manufacturing processes will consistently produce a product that meets predetermined specifications for quality and intended use. The Source Plasma establishment must monitor its processes/procedures to ensure that they continue to work as expected. [21 CFR 211.22]

The individual or unit performing QA activities coordinates, monitors, and facilitates all activities, including approval of all procedures or specifications that impact the safety, purity, and quality of Source Plasma products and those that prevent the release of unsuitable products. The QA unit ensures adequate laboratory facilities and manufacturing operations consistent with CGMP and applicable standards and ensures that staff follows them. The QA unit ensures that there is adequate quality control of routine on-line or in-process monitoring of manufacturing procedures. [21 CFR 211.22]

The guidance document, "Guideline for Quality Assurance in a Blood Establishment" contains a more complete discussion of our recommendations related to QA functions/activities relevant to blood establishment operations. http://www.fda.gov/cber/gdlns/gde_qa.pdf

A. Standard Operating Procedures (SOPs)

The unit or individual performing QA activities shall have the responsibility to review and approve written SOPs, including any changes. The QA program's various planned activities should provide confidence in the manufacture and overall quality of Source Plasma products. The Source Plasma establishment must have procedures in place to identify failures of Source Plasma to meet specifications and should correct those failures.

The Source Plasma establishment should evaluate the effectiveness of corrective actions implemented. Source Plasma establishments use various names when referring to these systems, such as error and accident reporting systems, incident reports, problem reports or logs, in-house problem reports (non-reportable) or biologic product deviations. In addition to maintaining records of product or process deviations, the Source Plasma manufacturer must also ensure that the following incidents are documented and investigated:

- Adverse Reactions
- Product Collection Fatalities
- Lookback Events
- Biological Product Deviations (BPD)

The manufacturer must ensure that the Source Plasma establishment complies with regulatory requirements for record maintenance, storage and required reporting.

During the inspection,
1. Verify that SOPs are available and followed for each system inspected. 2. Review records to verify that QA investigates, documents, and implements corrections as required for biological product deviations, unexplained discrepancies, failures of Source Plasma to meet specifications (e.g., products not stored under appropriate storage conditions or shipped at unacceptable temperatures), and adverse reactions resulting from Source Plasma collection in order to identify all factors contributing to the problem. The documentation must include conclusions of the investigation and follow-up. 3. Determine if there are any trends in deviations (reportable or non reportable) identified by the Source Plasma establishment. Note: A pattern of recurring problems may indicate an incomplete investigation or inadequate correction.

B. Adverse Reactions

The Source Plasma establishment must maintain a record of any donor reaction that it receives and must conduct a complete investigation and document the investigation findings. [21 CFR 606.170]

During the inspection,
Review records of adverse donor reactions.

C. Donor Fatalities

A Source Plasma establishment must report to CBER as soon as possible any complication of blood collection that results in a donor fatality. Within 7 days, the Source Plasma establishment must submit a written report of its investigation of the fatality to the Director, Office of Compliance and Biologics Quality. The Fatality Program Manager (HFM-650) usually receives initial notice within 24 hours of the fatality or, at least, by the next business day. [21 CFR 606.170 (b)]

If an investigator becomes aware of an unreported fatality during an inspection, contact the Fatality Program Manager, Division of Inspections and Surveillance 301-827-6220 as soon as possible to discuss the circumstances surrounding the incident and to confirm that the Source Plasma establishment should report the fatality.

Determine that the Source Plasma establishment conducted an adequate and complete investigation.

During the inspection,
Fatality follow up 1. Review the Source Plasma establishment's investigation. 2. Review donor records and if the Source Plasma establishment does

automated collection, also review the device records, maintenance log, and other relevant records.

3. Review both the initial notification to CBER and the 7-day written report. Often the fatality investigation is not completed in 7 days, so also review any report relevant to the investigation of the case that later became available. Determine if the firm reported accurate information to the Fatality Program Manager.
4. Review any corrective action and procedure to monitor its effectiveness.
5. Obtain a copy of the relevant records as indicated in the guidance document, "Notifying FDA of Fatalities Related to Blood Collection or Transfusion." http://www.fda.gov/cber/gdlns/bldfatal.pdf

Send a copy of the pertinent section of the EIR with exhibits to the Fatality Program Manager. Refer to the cover page of this document for the address.

D. Lookback

See Attachment G

E. Biological Product Deviations (BPD)

The investigation of all deviations, including BPDs, is an integral part of the Source Plasma establishment's QA system. Under 21 CFR 606.171, the licensed manufacturer must report to CBER any event associated with the manufacture, or any information relevant to the event, including testing, processing, packing, labeling, or storage, or with the holding or distribution of Source Plasma that may affect the safety, purity, or potency of a distributed product.

Events are required to be reported to CBER/OCBQ/DIS as soon as possible, but no later than 45 days from the date of discovery reasonably suggesting that a reportable event occurred. Under 21 CFR 606.171, the manufacturer who holds the biologics license and who had control over the product when the deviation or unexpected or unforeseen event occurred must report a BPD.

If a manufacturer contracts out any manufacturing step, that manufacturing step is performed under the manufacturer's control under the regulation. Thus, under 21 CFR 606.171(a), the manufacturer must establish a procedure for receiving information from that contract manufacturing facility of all deviations, complaints, and adverse events that may affect the product.

A *contract manufacturer* (i.e., performs, under contract, a step in manufacturing for another facility) must conduct manufacturing in accordance with all applicable regulations.

Ensure that any reportable events that may have occurred have been reported to CBER.

ORA investigators have direct access to BPD information through CEARS (CBER Error and Accident Reporting System). Instructions for accessing the system are posted on the CEARS Intranet web page. Refer questions to the Email address: bp_deviations@cber.fda.gov

To facilitate industry reporting of BPD, CBER developed a standardized reporting format

(FDA Form 3486) with both hard copy and electronic reporting. CBER encourages electronic reporting.

Website: http://www.fda.gov/cber/biodev/biodev.htm
Email address: bp_deviations@cber.fda.gov

Prior to conducting an inspection, investigators should review the establishment's BPD submissions in CEARS. Deviation codes may indicate systems that the investigator will want to examine more closely for patterns or trends. Otherwise, select a representative sample of reports to verify the adequacy of the firm's corrective action.

During the inspection,
1. Evaluate both reportable and non-reportable incidents or problem reports and verify the adequacy of any corrective action implemented by the Source Plasma establishment. 2. Verify that the Source Plasma establishment filed all reportable biological product deviations. (Contact OCBQ/DIS if clarification regarding BPD reporting is required.)

Source Plasma establishments are expected to follow-up on all reported BPDs with documentation of investigations and/or corrective actions. It is CBER's current thinking that a reportable event that has been identified, investigated, and corrected need not be included as a Form FDA 483 observation.

F. Donor Record Files

The manufacturer must ensure that the Source Plasma establishment maintains all required records applicable to Source Plasma manufacture consistent with regulatory requirements for record maintenance and storage. QA should ensure that records are accurate and provide a complete history of all work performed. [21 CFR 606.160 and 640.72]

The Source Plasma manufacturer must have separate and complete donor records (referred to as a donor record file) of all initial and periodic examinations, tests, laboratory data, interviews, etc. related to donor eligibility, product collection, immunization, and laboratory testing. [21 CFR 640.72]

During the inspection,
Review the records and verify that they contain the following information: 1. Initial and annual physical examinations and consent for plasmapheresis and immunization, as applicable [21 CFR 640.72] Note: See Attachment I - Infrequent Plasmapheresis Collection program. 2. Donor screening test results, e.g., hematocrit, temperature, blood pressure, pulse, donor weight, total protein, and donor medical history interviews [21 CFR 640.63] 3. Tests for communicable diseases and results of 4-month syphilis and serum protein electrophoresis testing and review [21 CFR 640.65] 4. Records of immunization, if applicable [21 CFR 640.66] 5. A cross-reference to unit(s) of Source Plasma collected from the donor [21

CFR 640.72]

6. Reason(s) for donor deferral, including red blood cell loss [21 CFR 606.160]
7. The reason Source Plasma was determined unsuitable [21 CFR 640.72] Donor reactions that occurred on or after leaving the premises [21 CFR 640.72] Collection volume

G. Equipment

The Source Plasma establishment's QA procedures should ensure:

1. Appropriate calibration, cleaning and preventative maintenance of equipment according to manufacturer's recommendations and/or SOPs;
2. Qualification of equipment and process validation, as necessary, including after repairs, ensure that equipment functions properly;
3. Computer systems used in manufacturing comply with 21 CFR 211.68 and 21 CFR 606.60
4. Computers, software, and interfaces used in the manufacture of Source Plasma are validated prior to implementation, qualified at the location where used, and revalidated as required.

During the inspection,
Review records and procedures the Source Plasma manufacturer used to assure that equipment performed as it was designed, including validation, as necessary, maintenance and periodic monitoring, if required.

H. Validation

QA should ensure that the Source Plasma establishment has procedures for conducting process validation and for assessing the need for revalidation. QA should also monitor validated processes to ensure that they continue to work as expected.

I. Manufacturer's Audit of Quality Assurance

A Source Plasma establishment should periodically evaluate its QA program to determine if it is effective in detecting, correcting, and preventing problems.
Refer to the Guideline for Quality Assurance in Blood Establishments.
http://www.fda.gov/cber/gdlns/gde_qa.pdf

ATTACHMENT B

DONOR ELIGIBILITY SYSTEM

This system identifies the Source Plasma establishment's procedures intended to protect the donor's health and ensure product safety. Donor eligibility requirements for manufacture of Source Plasma are found in 21 CFR 640.63. Part VI of this compliance program lists guidance documents and memoranda recommending additional donor eligibility requirements for Source Plasma donation.

A. Medical Supervision

Source Plasma regulations require a qualified licensed physician be on the premises when donor eligibility is determined, immunizations are occurring, whole blood is being collected, and red blood cells are being returned to the donor. [21 CFR 640.62] A Source Plasma establishment may have an approved physician substitute training program and may train an individual to perform some of the duties of a physician. Attachment H gives additional information about physician substitutes (PS).

Duties of physician substitutes often include the following: initial medical and physical examinations of new donors; annual physical examinations of repeat donors; evaluation of donor reactions and providing appropriate therapy as prescribed by the Source Plasma establishment's SOPs; performing immunizations (except Red Blood cell immunizations); counseling donors; and reviewing collection records and accumulated laboratory data to determine a donor's continued suitability for plasmapheresis.

During the inspection,

1. The physician must be qualified and licensed.
2. If the establishment uses a physician substitute, confirm that
   a. The establishment has a CBER-approved PS program.
   b. The PS meets the criteria identified in the approved program.
   c. Each PS received training for the duties performed in each Source Plasma establishment.

B. Obtaining Informed Consent

The Source Plasma establishment must obtain written informed consent for Source Plasma collection after a qualified, licensed physician or physician substitute has clearly explained the hazards of each procedure in which the prospective donor will participate: manual collection, automated plasmapheresis, immunization with an antigen, and participation in special collection programs approved by CBER; e.g., collection of Source Plasma from coagulant factor-deficient donors. Confirm that the donor is given an opportunity to ask questions and to decline participation. [21 CFR 640.61]

During the inspection,

1. Review the informed consent process to determine if it contains a simple explanation of the plasmapheresis procedure and the risks involved, such

During the inspection,
as infiltration, infection, and loss of red blood cells. 2. For automated operations, the informed consent may include the risk of possible anticoagulant reactions. 3. For manual operations, the informed consent must include the risk of inadvertently receiving another donor's red blood cells and the possibility of experiencing a hemolytic transfusion reaction. [21 CFR 640.61] 4. For immunization programs that use licensed vaccines, the informed consent must explain the risks associated with receiving the vaccine. [21 CFR 640.61] **5.** For participation in a red blood cell immunization program, CBER recommends that the informed consent include the risk of developing unexpected antibodies and the possibility of delays in blood transfusion or organ transplantation.

Note: CBER recommends that only men or women incapable of bearing children participate in a Red Blood Cell immunization program.

See the following guidance document for additional information:
http://www.fda.gov/cber/bldmem/031495.pdf
http://www.fda.gov/cber/gdlns/infrmdcnsntplsm.pdf

C. Donor Screening

The Source Plasma establishment must implement a system that positively identifies all donors (usually a photograph) and that relates the donor directly to the products collected and to the donor's accumulated records and laboratory data. The method used should prevent conditions that allow a prospective donor to impersonate another person or donate when not eligible, e.g. missing or poor quality photos, duplicate files, or acceptance of a deferred donor under a different name or social security number.

The Source Plasma manufacturer must determine donor eligibility, to include physical examinations, and medical screening, according to its SOPs and applicable FDA requirements. [21 CFR 640.63 and 640.65]

1. Identify yourself to the donor and explain that observing the screening process is part of a routine inspection. Ask the donor's permission to observe the screening process and give the donor a clear opportunity to refuse. If the donor refuses, make the request to another donor.

   Note: If management questions FDA's authority to observe donor screening, explain to management that observing the screening process is part of conducting the inspection of a Source Plasma establishment in a manner that is reasonable under the circumstances and, therefore, authorized by law. Follow the procedures in IOM section 514 (Inspection Refusal) if management refuses to permit observation.

2. The Source Plasma establishment should explain the donation process in a confidential manner so donors may make an intelligent and informed decision regarding whether to

participate in the donation procedure. The process must provide the donor with an opportunity to refuse the procedure. The method should ensure comprehension of the information presented and confidentiality. Source Plasma establishment must have appropriate procedures if collecting Source Plasma from hearing or vision-impaired donors, from donors who speak English as a second language, or from donors who may have a reading difficulty.

3. A third party; e.g., a translator may assist in the interview process. To ensure confidentiality and full disclosure of information by the donor, CBER recommends that Source Plasma establishment not use the donor's friends or relatives as the third party. This third party should understand the confidential nature of the information discussed and agree not to disclose it to anyone. The third party may not complete the questionnaire.

   The Source Plasma establishment must incorporate all screening procedures in its SOPs, including criteria for use of a third party. Donor records should indicate participation of a third party in the donor screening process.

During the inspection,

1. Observe one or more physicals.
2. Verify that medical examinations and physicals are conducted according to the SOPs and applicable FDA requirements and at the proper intervals. [21 CFR 640.63(a), (b)]
3. Personnel should adequately respond to donor questions or refer questions to the appropriate medical personnel, as necessary.
4. Review the Source Plasma establishment's procedure for determining a donor's good health on the day of donation for consistency with the requirements in 21 CFR 640.63 and current CBER recommendations regarding donor eligibility.
5. Verify that the physician / physician substitute reviews a total plasma or serum protein determination and serum protein electrophoresis or equivalent test to determine immunoglobulin composition, syphilis test results, and the donor's accumulated laboratory data within 21 days of collection of the initial and 4-month test samples.

   The physician / physician substitute must certify the donor's eligibility for immunization and /or continued plasmapheresis on a form designated by Source Plasma establishment.
6. The Source Plasma establishment should provide AIDS educational material, including information about high-risk activities, to donors at each visit. The Source Plasma establishment should have and follow its SOPs pertaining to any unexplained donor weight loss.
7. Confirm that the Source Plasma establishment performs all required screening tests (temperature, pulse, blood pressure, total serum or plasma protein and hematocrit or hemoglobin) in determining donor eligibility. [21 CFR 640.63] The establishment's SOPs may require additional tests not specifically required by FDA, such as periodic drug screening.

During the inspection,
8. Confirm that the Source Plasma establishment calibrates and maintains all equipment used in donor screening according to the device manufacturer's instructions and its SOPs and runs proper quality control according to the equipment manufacturer's instructions. 9. Verify that Source Plasma donors weight at least 110 pounds. 10. The donor's weight determines the amount of Source Plasma the manufacturer may collect in a manual procedure. In an automated procedure, CBER must specifically approve the collection volume. 11. Review a sufficient number of records to determine if the Source Plasma establishment only collects Source Plasma from donors with acceptable health history and screening test results, unless the establishment has amended its BLA to collect Source Plasma under a special collection program(s). 12. Confirm that the Source Plasma establishment collects Source Plasma from infrequent donors no more often than once every 4 weeks. For additional discussion of infrequent plasmapheresis, see Attachment I. 13. Review the Source Plasma establishment's procedure to prevent cross donation. Cross donation occurs when (a) an individual donates at more than one Source Plasma establishment or blood collection facility in a geographic area concurrently, (b) donates at one establishment although permanently or temporarily deferred at another, or (3) donates at a frequency that would be injurious to the donor's health. Review sufficient records to confirm that the Source Plasma establishment's procedures are adequate to identify donors and to prevent cross donation.

D. Donor Eligibility for Special Collection Programs - Attachment I

A manufacturer must have an approved BLA supplement to collect Source Plasma from special donor populations. Special collection programs include,

- Pre-Existing Antibody Collection
- Disease State and "High-Risk" Donor Collection
- Immunization
- Infrequent Plasma Collection

E. Donor Eligibility for Source Leukocyte / Therapeutic Exchange Plasma - Attachment K

F. Donor Deferral

The Source Plasma establishment must have specific procedures to defer donors who are determined ineligible for Source Plasma collection due to (a) medical history, (b) physical

examination, or (c) a positive screening test(s) for evidence of a communicable disease agent(s) identified in 21 CFR 610.40 (HIV-1 and 2, hepatitis B virus, hepatitis C virus and syphilis). [21 CFR 606.100(b)(20), 610.41] Note: Be aware that under special collection programs, manufacturers may collect Source Plasma from ineligible donors. See Attachment I.

The Source Plasma manufacturer must keep a record of deferred or ineligible donors so that products from such donor are not distributed. [21 CFR 606.160(e)] Most Source Plasma manufacturers verify the deferral status of new or returning donors prior to collection.

Manufacturers may ship Source Plasma collected prior to a donor's reactive syphilis serologic test result and donations determined to have a biologic false-positive syphilis test result. A donor may continue plasmapheresis after the donor's serologic test for syphilis tests non-reactive. [21 CFR 640.65]

During the inspection,
1. Review the Source Plasma establishment's procedures and criteria for donor deferral for compliance with 21 CFR 606.160(e) and 610.41. 2. Review records and observe operations to verify that the Source Plasma establishment accurately records donor screening deferrals, testing deferrals, and post donation information. 3. Confirm that the Source Plasma establishment accurately enters, either electronically or manually records, all causes of temporary or permanent deferrals. 4. The Source Plasma establishment should have procedures/computer programs to identify discrepant and/or duplicate donor information and procedures to prevent release of unsuitable products. 5. Determine if the establishment appropriately corrects and/or merges discrepant or duplicate records according to its SOPs. 6. Review records to determine if the Source Plasma establishment inappropriately released unsuitable Source Plasma.

G Notifying Ineligible Donors

A Source Plasma establishment must have procedures to notify a Source Plasma donor of a change in donation status whenever the Source Plasma establishment determines that the donor is ineligible for future donations based on the requirements in 21 CFR 640.63 or the results of required testing for communicable disease agents in 21 CFR 610.40. [21 CFR 630.6] The SOPs must include the method for notifying the donor, including follow-up if the initial attempt at notification fails. [21 CFR 606.100(b)(20)] Note: The donor may meet requirements to participate in a special Source Plasma collection program.

During the inspection,
Review a sampling of records with repeat reactive test results to determine if the Source Plasma establishment performs supplemental testing and notification to donors as required in 21 CFR 630.6.

H. Donor Re-Entry Algorithms

A Source Plasma establishment may re-enter donors previously deferred because of a positive test result for a required communicable disease agent after it finds the donor is otherwise eligible by a re-qualification method or process acceptable to FDA and the donor is otherwise suitable. Most Source Plasma establishments, however, do not re-enter donors.

The following blood memoranda identify acceptable procedures to re-qualify a previously deferred donor for further Source Plasma collection.

- HBsAg Part VI http://www.fda.gov/cber/bldmem/120287.pdf
- HCV Part VI http://www.fda.gov/cber/bldmem/080593.pdf
- HIV Part VI http://www.fda.gov/cber/bldmem/hiv042392.pdf

During the inspection,
Identify donors that the Source Plasma establishment re-entered and confirm that the establishment performed donor re-entry according to the acceptable methods or processes identified in the above documents. [21 CFR 610.41]

ATTACHMENT C

PRODUCT TESTING SYSTEM

Testing of Source Plasma for evidence of communicable disease agents must be conducted correctly and monitored closely to ensure the quality and safety of products. Manufacturers must test each donation of Source Plasma for the following communicable disease agents as required under 21 CFR 610.40:

- Human Immunodeficiency Virus, types 1 & 2
- Hepatitis B Virus
- Hepatitis C Virus

The manufacturer must also test donors for syphilis, total plasma or serum protein, and immunoglobulin composition of plasma or serum, initially and every four months. [21 CFR 640.65(b)]

Further testing of each reactive donation, using screening and supplemental tests approved by FDA for such use is also required. Source Plasma establishments may contract part or all of the communicable disease testing to an outside testing laboratory. The contract, testing laboratory must register with FDA and be certified by the Centers for Medicare and Medicaid Services (CMS) or has met equivalent requirements as determined by CMS to perform infectious disease testing. The Source Plasma establishment must ensure that the contract laboratory is registered with FDA and that laboratory testing complies with 21 CFR 610.40 (a), (b), (e) and (f).

The laboratory must perform required testing for communicable disease agents using screening and supplemental test kits FDA has approved for such use. Serological tests for syphilis should be labeled for use in donor screening. A list of currently licensed HIV and hepatitis test kits is on the Internet at http://www.fda.gov/cber/products/testkits.htm

A Source Plasma establishment that does its own testing for evidence of a communicable disease agent must retain testing records as required in 21 CFR 606.160(d). A manufacturer that sends such testing to an outside laboratory must have test results; i.e., reactive, nonreactive, positive, negative or indeterminant in written form (hard copy or available electronically) prior to releasing Source Plasma for further manufacture.

A. Communicable Disease Testing - On-Site

This section applies to inspection of Source Plasma establishments that perform on-site testing for required communicable disease agents. The following inspection guidance supplements the comprehensive, "Guide to Inspections of Infectious Disease Marker Testing Facilities," October 1996. http://www.fda.gov/ora/inspect_ref/igs/infdis.html

During the inspection
1. Observe actual testing practices and procedures. Choose a time when personnel and/or supervisory oversight are at a minimum level. Verify that appropriate controls are used, that samples and controls are diluted properly, that the time and temperature of incubation are accurate and that instrument

and equipment settings are correct during testing.

2. Verify that the Source Plasma establishment performs equipment maintenance according to the manufacturer's recommendations and the firm's SOPs.
3. Confirm that all testing problems are adequately investigated, resolved, and documented.
4. If unable to observe infectious disease testing, then at a minimum, compare the establishment's test procedures with the test kit inserts, test equipment user manuals, and reagent inserts.
   Review the package inserts for the lot of test kits and reagents in current use instead of those on file. Investigate any noncompliance noted between inserts or manuals and the firm's procedures. Discuss any questions with CBER/ Division of Emerging Transfusion Transmitted Diseases (301-827-3008).
5. Review as many required infectious disease test records as the inspection permits, extending the review as necessary depending on findings.

   Consider both the size of the firm and its compliance history. If possible, select records from a time period when problems are more likely to occur, such as holidays, on evening shift, at installation of new equipment, or when there is new management or personnel. Investigate unusual test results, such as low values and invalidated test results.
6. Select a representative number of reactive test results for each required disease agent. Track the units from donor screening, product collection, donor deferral, product quarantine, storage, and disposition to verify appropriate handling of products and required recordkeeping.
7. Observe procedures for handling samples and labeling processing trays. Assess whether the procedures are adequate to prevent sample mix-ups. The laboratory must store samples as specified in the test kit manufacturer's directions.
8. Ensure that the sample requirements (anticoagulant, age of sample, quantity, storage temperature, especially if testing is delayed, etc.) are met.

   The Source Plasma establishment must qualify automated sampling equipment and positive identification systems to ensure proper identification of samples and test results.
9. Evaluate the Source Plasma establishment's laboratory quality control program. Determine if all laboratory equipment is qualified, calibrated and maintained as required by user manuals, maintenance manuals and the Source Plasma establishment's standard operating procedures. [21 CFR 606.60]

B. Invalidation of Test Results

Evaluate the Source Plasma establishment's procedures for invalidating a test result for consistency with the recommendations in the document, "Guidance for Industry: Revised Recommendations Regarding Invalidation of Test Results of Licensed and 510(k) Cleared Bloodborne Pathogen Assays Used to Test Donors," dated July 11, 2001. http://www.fda.gov/cber/gdlns/bldbrn.htm This guidance incorporates provisions of the Clinical Laboratory Improvement Act of 1988 (CLIA) for invalidation of test results based on CLIA external control requirements.

Laboratories or facilities that do testing may invalidate a reactive test result **ONLY IF** the assay run in which a sample is tested either fails to meet test kit package insert acceptance criteria **OR** the firm failed to do testing according to the test kit instructions; e.g., using compromised reagents or faulty equipment. If test kit package insert instructions are met, but CLIA control requirements are not met, the laboratory may invalidate only non-reactive results, but **MAY NOT** invalidate any reactive results. If an initially reactive specimen tests reactive on one or both of the two repeat duplicate tests, the sample is repeatedly reactive and the testing laboratory should manage the results as indicated in the guidance document. When a negative or non-reactive test result is legitimately invalidated, re-test the sample singly and that result, if valid, is the test of record.

The testing facility should document all incidents of invalidation including:

- The basis for invalidation
- The details of an investigation
- The outcome of the investigation, and
- If indicated, any corrective action taken

NOTE: The testing facility should take these actions prior to repeat testing of a donor sample.

During the inspection,
Review all records of invalidation of test results for consistency with test kit manufacturer's directions for use and CBER recommendation. Notify CBER/Division of Inspection and Surveillance at 301-827-6220 if the firm uses other criteria to invalidate test results and determine donor eligibility.

ATTACHMENT D

QUARANTINE / STORAGE / DISPOSITION SYSTEM

A. Quarantine

The Source Plasma establishment must have control of the Quarantine/Storage/Disposition System to prevent the distribution of any unsuitable product. The Source Plasma establishment must quarantine Source Plasma products that, test reactive for required communicable diseases agents, that are awaiting additional more specific testing (21 CFR 606.40), that were collected under a high-risk collection program(s), or that meet the requirements for HIV lookback under 21 CFR 610.46.

The Source Plasma establishment must also quarantine other Source Plasma products (nonreactive for evidence of a communicable disease agent) that it determines unsuitable for use.

During the inspection,

1. Examine records to determine if the Source Plasma manufacturer quarantined Source Plasma products appropriately.
2. Evaluate the firm's procedure for removing products from quarantine; e.g., returning product to inventory after performing additional testing.
3. Verify that records identify the individual who removed products from quarantine, the date removed, and the reason for the removal. [21 CFR 606.160]
4. Confirm that after collection, the establishment immediately stores and maintains Source Plasma at the appropriate temperature and that the Source Plasma establishment documents the temperature. [21 CFR 610.53, 640.69, 640.74]

   Injectables: -20º C or colder

   Noninjectables: temperature appropriate for the intended use

   Source Plasma Liquid: 10º C or colder, unless otherwise approved by CBER
5. If Source Plasma for injectable use was not stored or shipped at appropriate temperatures, verify that the Source Plasma establishment re-labeled the product "Source Plasma Salvaged" consistent with 21 CFR 640.76(a)(1) or (b), unless an exception under 21 CFR 640.76(a)(2) applied or CBER confirmed that no re-labeling was required.
6. Review the establishment's distribution records to determine traceability of all Source Plasma products and maintenance of records according to 21 CFR 606.165 and 640.72.
7. Verify that the establishment releases Source Plasma for distribution only after it receives and reviews written or computerized test results for the Source Plasma products. [21 CFR 606.100(c)]

   Note: CBER approval is not required to ship products under quarantine, prior to completion of PCR or NAT testing, to other locations. (Source Plasma establishments, fractionators, or off-site storage locations) operating under the same license. In addition, Source Plasma establishments may ship products,

During the inspection,
under quarantine, pending PCR or NAT testing to an independently owned, unlicensed, off-site storage location without CBER approval. However, CBER approval is required if the Source Plasma establishment wishes to ship products prior to completion of PCR or NAT testing, to Source Plasma establishments, fractionators, or off-site storage facilities operating under a different license.

B. Equipment

All equipment used in Source Plasma manufacture must meet the requirements of 21 CFR 606.60.

During the inspection,
Verify that all storage and temperature monitoring equipment is calibrated and maintained per manufacturer's instructions. **Note:** After installation and qualification of a central temperature monitoring system, CBER may permit an alternate procedure from the daily comparison of the internal thermometer to the recording chart/device.

C. Shipment

The Source Plasma establishment shall ship Source Plasma at a temperature appropriate for manufacture of the final product. [21 CFR 600.15, 640.76(b)]

- Injectable: at –5ºC or colder
- Noninjectable: at 10ºC or colder or as indicated in an approved BLA supplement

Source Plasma for injectable use kept under continuous temperature monitoring requires no inspection for evidence of thawing prior to issue, provided temperature records indicate appropriate storage temperatures at –20°C or colder. [21 CFR 640.69(c)]

Source Plasma Liquid shall meet the requirements of 21 CFR 640.74. Prior to issue, the Source Plasma establishment must immediately inspect each container for abnormal color, physical appearance or indication of microbial contamination.

The Source Plasma manufacturer shall re-label Source Plasma stored at unacceptable temperature as "Source Plasma Salvaged," except as provided in 21 CFR 640.76(a)(2). The manufacturer must also maintain appropriate records identifying the units involved, their disposition and an explanation of the conditions that caused the unacceptable temperature exposure. [21 CFR 640.76(a)-(c), 640.70(b)]

During the inspection,
Confirm that the Source Plasma establishment ships products according to regulations.

D. Imported Blood and Blood Components

Currently, no foreign firm holds a biologics license to manufacture Source Plasma.

During the inspection,
1. Determine if the Source Plasma establishment received plasma products identified as “import for export.” Contact HFM-610 to verify that CBER approved the ‘import for export’ shipment pursuant to section 801(d)(4) of the FD&C Act. 2. Determine if the establishment received from outside the United States, returns of Source Plasma or rejected Source Plasma. Examine re-importation records associated with such products for signs of counterfeit imported products.

For further information, request Compliance Program 7342.007, “Examination of Blood and Blood Components Offered for Import” from CBER/OCBQ/DCM, HFM-610, (301)-827-6201.

ATTACHMENT E

PRODUCT COLLECTION AND PROCESSING SYSTEM

This system covers the Source Plasma establishment operations from collection through processing/labeling.

CBER approves a Source Plasma establishment to collect Source Plasma by manual or automated apheresis methods under various Source Plasma collection programs. The Source Plasma establishment may collect Source Plasma from donors only twice in a 7-day period, and at a 2-day interval. Donors who participate in an infrequent plasmapheresis collection program may donate no more frequently than once every four weeks. Infrequent plasmapheresis donors should meet Whole Blood donor suitability requirements and weigh 110 pounds. Currently, CBER approves infrequent plasmapheresis programs as a variance under 21 CFR 640.120

The collection procedures must ensure that the appropriate volume of Source Plasma is collected and that the maximum feasible volume of red blood cells is returned to the donor. [21 CFR 640.65] Overbleeding donors during manual collection and/or failure to return red blood cells due to technical difficulties during automated plasmapheresis may require temporary deferral of donors. [21 CFR 640.63]

The Source Plasma establishment must describe its collection method(s) in SOPs. Source Plasma collection must meet the requirements in 21 CFR 640.64 and 640.65.

The Source Plasma establishment must immediately store and maintain Source Plasma consistent with its intended use. It must store injectable products at - 20ºC or colder (except Source Plasma Liquid) and noninjectable products, at a temperature appropriate for the final product. [21 CFR 640.69(b), (c) and 640.70(a)(3), (11)(b)]

All products and records must be traceable to the donor. [21 CFR 606.160(c), 640.72(b)]

For additional information regarding Source Plasma collection, consult the following document at http://www.fda.gov/ora/inspect_ref/igs/Source_Plasma/default.htm.

A. Venipuncture

The Source Plasma establishment personnel must prepare the skin at the site of phlebotomy thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. [21 CFR 640.64(e)]

During the inspection,
Observe several phlebotomists as they prepare the venipuncture site. Verify that each phlebotomist prepares the venipuncture site consistent with the establishment's SOPs. Critical steps in preparing the skin for venipuncture include, • Sufficient time and vigor of scrubbing - key factors in removing superficial microbes. • Applying a bactericidal agent according to the reagent manufacturer's instructions. • No touching of the prepared area with fingers or other non-sterile object,

During the inspection,
including donors bending their arms.

Acceptable procedures for preparing the venipuncture site are on the Internet at http://www.fda.gov/cber/infosheets/armpreprev.htm

B. Collection Methods

CBER approves both manual and automated SOPs for collection of Source Plasma. Manufacturers should have a procedure to identify and prevent overbleeds. Overbleeding occurs when the amount of Source Plasma exceeds what may be collected at one time from a donor or the donor donates more frequently than twice in a 7-day period

1. Automated Collection

   CBER has cleared several fully automated, stand-alone or concurrent plasma collection systems for plasma collection. Devices cleared to collect plasma products as a by-product of plateletpheresis or red blood cell apheresis are used in blood bank or blood center operations. Most Source Plasma establishments use the following stand-alone devices:

   - Baxter Healthcare Corp. - Autopheresis-C Plasmapheresis System
   - Haemonetics - PCS Plasma Collection System
   - COBE/Gambro - Trima

During the inspection,
1. Review the SOPs for automated collection of Source Plasma. Verify that the Source Plasma establishment collects Source Plasma according to its approved procedures and the collection device manufacturer's instructions. 2. Observe Source Plasma collection to assess the adequacy of employee training. The staff should be able to explain error messages and take appropriate action. **Note:** CBER recommends the following operator to device ratio: 1 trained operator may operate 6 devices and 1 trainee operator may operate 4 devices under the supervision of a trained operator. The trainee's 4 devices should be included within the trained operator's 6 devices so that the trained operator does not exceed the number of devices that the operator may safely oversee. 3. Become familiar with device safety alarms. Verify that employees do not override or bypass the alarms without taking corrective action as indicated in the device manual(s). 4. Review each collection device record or log to identify any problems with the device. The record or log should include all warning alarms and problems in returning red blood cells. The record or log often identifies problems with disposable collection sets. 5. Verify that the Source Plasma establishment performs and records routine maintenance according to the device manufacturer's instructions.

During the inspection,

6. Confirm that the Source Plasma establishment has procedures to ensure that collection devices operate properly after software changes and following repairs. [21 CFR 606.60] **Note:** Computer software in collection devices can frequently be changed using manufacturer upgrades.
7. Review donor record files to verify that the Source Plasma establishment collects the appropriate volume of plasma specifically approved for the device. [21 CFR 640.65]

   The establishment may use a device-specific approved nomogram or plan to determine the amount of plasma to collect.

   A nomogram may use several criteria to determine the collection volume; e.g., the donor's gender, weight, height, and hematocrit. CBER developed a simplified nomogram that determines the maximum collection volume or weight of plasma based only on the weight of the donor. **Note:** CBER recommended that use of the simplified nomogram, precludes use of any other nomogram in the Source Plasma establishment, including those provided by the device manufacturer. Consult the guidance document at http://www.fda.gov/cber/bldmem/110492.pdf

   The Source Plasma establishment should have a procedure to track red blood cell loss. Verify that the employees appropriately defer donors who failed to have their red blood cells returned, unless exempt under 21 CFR 640.63. **Note:** Any person who has donated one unit or more of Whole Blood (or who has lost the equivalent amount of red blood cells due to technical difficulties during an automated plasmapheresis procedure) must not serve as a donor of Source Plasma for 8 weeks. [21 CFR 640.63(e)]

For additional information, consult the guidance documents at the following websites**:**

http://www.fda.gov/cber/bldmem/mem120495.pdf
http://www.fda.gov/cber/bldmem/110492.pdf

2. Manual Collection

A Source Plasma establishment that uses a manual method must collect and process Whole Blood for Source Plasma according to the requirements in 640.65(b)(4) – (7), 640.68 and the establishment's approved SOPs. The SOPs should describe in detail the collection procedures, including:

- Donors should participate in the procedure for returning red blood cells.
- The Source Plasma establishment should adequately mix the contents of the collection bag during collection.

During the inspection,

a. Review donor record files to confirm that the interval between donations is consistent with regulations. [21 CFR 640.65]
b. Review the Source Plasma establishment's procedures for returning the

During the inspection,
maximum amount of red blood cells to the donor. [21 CFR 640.66(b)(7)] Observe as many employees as possible collect Source Plasma to ensure that staff is following the establishment's procedures. c. Verify that double bagging (collection of the second bag of whole blood prior to the return of the red blood cells from the first bag collected) does not occur. [21 CFR 640.65(b)(6)] d. Verify that the Source Plasma establishment has a procedure to identify and prevent overbleeding; e.g., monitoring scales after adjustments or repairs, as necessary. Note: Review Whole Blood weight records to determine the number of overbleeds by volume per day. e. Confirm that appropriate procedures exist for plasma pooling to prevent cross-pooling. [21 CFR 640.69] f. Investigate any incidents of incorrect red blood cell infusion. Any incident of incorrect red blood cell infusion is a serious departure from the Source Plasma establishment's SOPs. The Source Plasma establishment should have procedures to provide the donor who received the incorrect red blood cells appropriate emergency medical attention. g. Confirm that the Source Plasma establishment's procedures properly defer each donor involved in the incident. The manufacturer must defer donors who did not receive their own red blood cells, from further collection for eight weeks. The manufacturer must also defer donors who received incorrect cells, for 1 year because those donors received a blood transfusion.

C. Labeling

Product labels must meet the requirements of 21 CFR 640.70 and 640.74. CBER reviews most product labels prior to use. The manufacturer, however, may submit labels for collecting disease-associated Source Plasma in its annual report of minor changes.

D. Source Plasma Collection Programs (See Attachment I)

- Immunization Program
- Pre-existing Antibody Collection Program
- "High-Risk" or Disease State Donor Collection Program
- Infrequent Plasmapheresis Collection Program

E. Source Plasma Collection Programs (See Attachment K)

- Source Plasma and Therapeutic Exchange Plasma

ATTACHMENT F

COMPUTERS

Blood establishments may use computer systems for a variety of operations. They may utilize a complex, integrated computer system with a donor software module or they may use a single software module. Computerized operations may include:

- Storing, updating, and accessing donor history information, donor deferral records and distribution records.
- Accepting, storing, and interpreting test results. Results may be entered manually or by electronic file transmission from the test instrument or laboratory data management system.
- Releasing Source Plasma for distribution.

Determine which operations are computerized and how the user validated the computer system on-site to demonstrate that it performs the intended functions accurately and reliably.

A. Requirements for Source Plasma Establishment Computer Software

All software, including software developed in-house, used to manufacture blood and blood components (including Source Plasma), to maintain data for making decisions about donor eligibility, or to release products for further manufacture are medical devices under Section 201(h) of the FD&C Act. The device provisions such as: registration as a device manufacturer, product listing, medical device reporting, compliance with the quality system regulation, and pre-market notification 510(k) or application apply to the device software manufacturer. Only blood establishment computer software that is 510(k) cleared or has pre-market approval (PMA) should enter interstate commerce.

FDA has previously advised blood establishments to transition to either a cleared software product or to one for which a manufacturer was actively pursuing clearance or to submit a plan to convert its in-use computer software.

Software manufacturers/developers who distribute their products interstate are subject to the Quality System Regulation requirements (21 CFR 820) and pre-market approval requirements.

Source Plasma establishments that developed software for their own use but that did not ship the software interstate are subject to the Quality System Regulation requirements (21 CFR 820), the CGMP for Blood and Blood Components (21 CFR 606), and the CGMP for Finished Pharmaceuticals (21 CFR 211).

Source Plasma establishments that use vendor-supplied software are subject to the CGMP for Blood and Blood Components and the CGMP for Finished Pharmaceuticals. Establishments are required to perform user validation to ensure that the software meets its intended use.

FDA deems a Source Plasma establishment that develops software for its own use as a medical device manufacturer and, therefore, subject to the Quality System Regulation**.**

Computer software developed by a Source Plasma establishment, but that is used by

outside consignees (not under the same license number), constitutes commercial distribution and interstate commerce, and requires a 510(k). Also use of software/data by sites under the same license number may require submission of a 510(k) if the software / data crosses state lines.

During the inspection,
Verify that the Source Plasma establishment uses only 510(k) cleared software. Contact CBER / OBRR / DBA / Devices Review Branch, HFM-390, for guidance regarding computer software. A list of 510(k) cleared blood bank software is posted at http://www.fda.gov/cber/products/510ksoft.htm

B. Inspection Code

Use the following medical device reporting codes when conducting inspections of computer software manufactures:

Establishment Type - MW
Product Code - 81M
PAC Codes: 42845A – Level 1; 42845B – Level 2; 42845C – Level 3 inspections

C. Programs and Computer Functions to Include in the Inspection

Criteria to consider when deciding which functions of the system to inspect:

1. The criticality of the functions controlled by the computer, (e.g. determination of product suitability for release)
2. Computer problems revealed by reviewing computer problem reports and biologic product deviation reports
3. Areas suggested for inspection after reviewing computer system change control records.

During the inspection,
1. Review the operator's manual. 2. Observe the use of the computer system. Observe manual data input, screen messages, error checking, etc. 3. Review the overall validation plan and procedures and the validation of critical programs and reports critical to the Plasmapheresis establishment's operations. Often validation is conducted at the corporate location. User validation of Source Plasma establishment software is required by 21 CFR 211.68(b). 4. Determine if the Source Plasma establishment validated the system prior to implementation. Determine if the establishment followed the manufacturers' instructions regarding installation and validation of upgrades. 5. Be alert to user customization of vendor supplied software systems. Customization is normally accomplished by a user setting certain parameters which affect how the software functions**.** Check the vendor's recommended configuration and review the validation of all deviations from the vendor recommended parameters.

During the inspection,

6. Determine if the Source Plasma establishment includes changes to software under written change control procedures and if it documents changes to the system. The establishment should document the change (who made the change, who authorized the change, and the effective date of the change).
7. Review the use of "work-arounds." Establishments may implement work-arounds when the system does not perform exactly the way the user requires and the software vendor recommends and/or the user develops procedures to circumvent the system's limitation. Determine the reason the work-around was created, whether it adequately addressed the situation and whether the work-around created any other problems.
8. Determine if the Source Plasma establishment monitors the functioning of the computerized system for errors and if it documents them and assesses their impact on operations and/or records.
9. The Source Plasma establishment should have written procedures for continuing operations when the computer system is not functional, in addition to procedures for data and system recovery in the case of system failure. It should periodically back up data and systems files and store them in a secure location.
10. Review the Source Plasma establishment's written policies for computer security and determine if the firm follows them. Source Plasma establishments that maintain electronic records must maintain the integrity of those records as required by 21 CFR Part 11. System access must be controlled to limit access to only authorized individuals. If a record is changed, the previous data, the person making the change, and the time the change was made must be documented electronically.

ATTACHMENT G

LOOKBACK

FDA regulations require lookback for HIV. [21 CFR 610.46] The lookback process addresses prior donations collected from donors who subsequently test HIV positive and requires that Source Plasma establishments perform the following:

- Quarantine in-house products previously collected from the donor.
  Note: Products may be stored at an offsite storage location or at a fractionation plant, but are not released for use. The Source Plasma establishment's procedures should define notification, quarantine, culling, and the final disposition of those products.
- Notify consignees to quarantine products in their inventory that are not pooled or further processed.
- Notify consignees of the results of further communicable disease testing.

See the guidance document, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products. http://www.fda.gov/cber/bldmem/hiv042392.pdf

During the inspection,
1. Review the SOPs to determine that lookback procedures comply with regulations. 2. Verify that the Source Plasma establishment notifies consignees to quarantine Source Plasma, Source Leukocytes and Therapeutic Exchange Plasma collected within 6 months prior to the positive test result if those products are not pooled or further processed, unless exempt under 21 CFR 610.46(c). **Note:** Source Leukocytes are processed within 24 hours of collection. Source Plasma is usually pooled within 6 months of collection. 3. Determine if the Source Plasma establishment investigated any deviations in testing procedures or donor deferral. If the event(s) were reportable, determine if the manufacturer notified CBER.

FDA issued guidance documents describing lookback recommendations at products reactive for hepatitis B virus, hepatitis C virus, hepatitis B core and Human T-Lymphotropic virus.

http://www.fda.gov/cber/bldmem/mem71996.pdf,
http://www.fda.gov/cber/gdlns/hcvlkbk.htm and
http://www.fda.gov/cber/gdlns/htlv-ii.pdf

ATTACHMENT H

PHYSICIAN SUBSTITUTES

A Source Plasma establishment may supplement its biologics license to request an alternative procedure under 21 CFR 640.120 to use an adequately trained physician substitute to perform some of the routine functions of a physician in the establishment. The educational requirements and job description or statement of responsibilities are part of the Physician Substitute Training Program. After CBER approval, the manufacturer may train individuals to function as physician substitutes in the Source Plasma establishment.

In general, the physician substitute:

- Should be a graduate of a recognized educational program (nursing, emergency medical technician or physician assistant) and currently licensed or certified in the state where employed. The physician substitute should maintain current certification in cardiopulmonary resuscitation.
- Should complete the Source Plasma establishment's training program and be determined competent by the establishment's medical director before assuming the physician substitute duties.
- Should have a periodic evaluation of performance of assigned duties in the Source Plasma establishment performed by the medical director.
- May evaluate, (1) normal healthy donors for both manual and automated apheresis procedures, and (2) donors in pre-existing disease and non-disease associated collection programs. These donors meet the eligibility criteria for Source Plasma collection.
- With additional training and under the direction of the medical director, may administer or supervise approved immunizations, except red blood cell immunizations.
- May administer Red Blood Cells, as an immunogen, but the physician must be on the premises.

Currently, a physician substitute's responsibilities may not include involvement in "high-risk," and disease-state Source Plasma collection programs.

Consult the following guidance documents for additional information.

http://www.fda.gov/cber/bldmem/081588.pdf

During the inspection,
Confirm that all physician substitutes in the Source Plasma establishment received training consistent with the approved training program for the duties the PS performs and meets the education and certification requirements of the program.

ATTACHMENT I

SOURCE PLASMA COLLECTION PROGRAMS

This attachment contains recommendations related to the review of BLA submissions to manufacture various Source Plasma products. To obtain additional information about these collection programs, consult the guidance documents as listed or for various program approvals, contact CBER, Division of Blood Applications, 301-827-3543.

A. Pre-existing Antibody Collection Program

CBER may approve a Source Plasma establishment to collect Source Plasma from donors who have a pre-existing antibody; e.g., antibody to Duffy red blood cell antigen (anti-Fya) or antibody to human leukocytes. Donors must meet all Source Plasma eligibility criteria.

During the inspection,
Verify that the Source Plasma establishment has notified CBER of various pre-existing antibody collection programs. The firm may submit those changes in its annual report of minor changes.

B. Pre-existing Disease-Associated Collection Program

A Source Plasma establishment may collect Source Plasma from donors who have pre-existing, disease-associated antibodies because of a previous exposure to certain diseases or cellular antigens; e.g., IgG antibody to Cytomegalovirus or anti-hepatitis A virus. Donors must meet all Source Plasma donor eligibility criteria. The manufacturer should inform donors that their participation in a special collection program depends on the level of antibody. A donor may immediately return to Source Plasma collection if the Source Plasma establishment no longer desires to collect the antibody. The manufacturer should notify CBER of the implementation of such programs in the establishment's annual report of minor changes.

Consult the Guide to Inspections of Source Plasma Establishments for a partial listing of disease-associated antibodies and the "Draft Reviewers' Guide for Disease Associated Antibody Collection Program," October 1995.

http://www.fda.gov/ora/inspect_ref/igs/Source_Plasma/default.htm
http:/www.gov/cber/gdlns/antbdyclcprgm.pdf

During the inspection,
Verify that the Source Plasma establishment collects Source Plasma from donors with pre-existing antibodies according to its SOPs.

C. Disease-State Collection Program

This program allows Source Plasma collection from donors who may not meet all Source Plasma eligibility requirements. These donors are generally feeling well and are not experiencing any active symptoms on the day of donation. The disease conditions under this

program require physician's authorization for collection. Some examples of disease state collections are antibody to Lyme disease or antibody to coagulation factors. The plasma is used for further manufacturing into in vitro diagnostic reagents.

Prior to implementing a disease-state collection program, the manufacturer must submit a supplement to the BLA. The supplement should include SOPs that define the donor selection criteria, labeling, quarantine procedures, and Source Plasma disposition.

The manufacturer should collect, handle, store, and distribute reagents, samples, and Source Plasma according to current biosafety guidelines established by FDA, Centers for Disease Control and Prevention (CDC) and /or Occupational Safety and Health Administration (OSHA).

During the inspection,
Confirm that the Source Plasma establishment follows its approved procedures and collects Source Plasma only from donors for which it has CBER approval.

D. "High-Risk" Donor Collection Program

This program allows Source Plasma establishments to collect Source Plasma from donors who have a positive test result for a communicable disease agent. The product may be used in research, or for in vitro tests, or development of therapeutic products. CBER pre-approves the SOPs and labeling for this program. Product collection, handling, storage, and disposition of samples and Source Plasma should be in accordance with current biosafety guidelines established by FDA, CDC and /or OSHA. For additional information, consult the following guidance documents.

http://www.fda.gov/cber/bldmem/041791.pdf
http://www.fda.gov/cber/bldmem/102689.pdf

During the inspection,
Review SOPs and confirm that the Source Plasma establishment collects product according to its approved SOPs and only from "high-risk" donors for which it has CBER approval.

E. Immunization Programs

A Source Plasma manufacturer may immunize donors using licensed products; e.g., tetanus or rabies vaccines, for collection of high titer antibody. If the program is consistent with the vaccine insert instructions, the manufacturer may supplement its BLA and distribute product within 30 days of CBER notification. Immunizations using red blood cells from a source approved by CBER in a BLA license application or supplement requires an inspection prior to use. Immunizations using unlicensed vaccines are conducted under an Investigational New Drug application. An inspection of a licensed firm prior to vaccine use, however, is usually not conducted.

During the inspection,
1. Confirm that the Source Plasma establishment has CBER approval for each

During the inspection,

immunization program, as required.

2. Confirm that Source Plasma donors meet eligibility requirements in 21 CFR 640.63 and that the immunization complies with 21 CFR 640.66.
3. Verify that the Source Plasma establishment's process for obtaining consent for immunization informs donors of the hazards of immunization appropriate to the immunizing agent used.

   The Source Plasma establishment should also inform donors immunized with red blood cells that they may develop atypical or unexpected red cell antibodies that may interfere with obtaining a compatible blood, organ or tissue transplant in the future.

   Note: CBER recommends that only males or females who are incapable of bearing children participate in red blood cell immunization programs.

   CBER recommends that donors not participate in more than one immunization program at a time.
4. For red blood cell immunizations, confirm that only a licensed qualified physician selects and schedules the antigen injection and evaluates the donor's clinical response. [21 CFR 640.66]

   A physician must be on the premises when immunizations are made. A physician substitute or other trained individual under a physician's supervision may administer immunizing agents.

   Donors who participate in a red blood cell immunization program should receive required and CBER recommended testing, initially and at periodic intervals.

   An immunized donor may return to normal Source Plasma collection if the donor fails to meet the titer requirement of the immunization program.
5. Confirm that the Source Plasma establishment uses only approved antigens or immunizing substances and that it handles and stores them appropriately.

   Promptly notify CBER, Division of Inspections and Surveillance (HFM-650) at 301-827-6220 if a Source Plasma manufacturer uses red blood cells that were not qualified.
6. If the Source Plasma establishment prepares red blood cells for immunization, review all Whole Blood donor and recipient / Source Plasma donor manufacturing records.
7. Review the system for tracking red blood cells from the Whole Blood donor to the red blood cell recipient / Source Plasma donor. Usually a lot numbering system is devised.
8. Review both the Whole Blood donor and recipient / Source Plasma donor viral marker test records for any reactive or positive infectious disease test results.

Consult the following guidance documents for additional information.

http://www.fda.gov/cber/bldmem/031495.pdf
http://www.fda.gov/cber/gdlns/imnztnsrcpl.pdf
http://www.fda.gov/cber/bldmem/070788.pdf

F. Infrequent Plasmapheresis Collection Program

A Source Plasma establishment may supplement its BLA to include Source Plasma collection from non-immunized donors, who meet whole blood donor suitability requirements, other than donation frequency, every four weeks or less frequently. The donor must weigh a minimum of 110 lbs. Note: If infrequent donors donate no more frequently than every four weeks, they do not require a physical examination or a total plasma or serum protein or immunoglobulin composition. The maximum annual number of Source Plasma collections from a donor and the volume collected at each donation are described in the following guidance documents:

http://www.fda.gov/cber/bldmem/031095.pdf
http://www.fda.gov/cber/bldmem/110492.pdf

A donor should not participate simultaneously in other blood or plasma collection programs and should not be a frequent apheresis donor. If an infrequent donor returns for donation in less than 4 week or donates more that the maximum annual volume of Source Plasma, the Source Plasma establishment should follow all Source Plasma donor eligibility requirements, including medical examination and plasma or serum protein tests prior to considering the donor eligible for another donation. [21 CFR 640.63]

During the inspection,
Confirm that the Source Plasma establishment is following its CBER-approved SOPs.

ATTACHMENT J

TYPES OF BLOOD ESTABLISHMENTS COVERED UNDER THIS PROGRAM

The blood establishments listed below must register with CBER and list each product that they manufacture as required by 21 CFR 607. Access the CBER Intranet to query the Blood Establishment Registration database to review registration information for active, inactive and pre-registered establishments. For additional information, consult the "Instruction for Completing the Blood Establishment Registration Form 2830," on the FDA Intranet, Forms Catalog.

1. Contractor

   Any person or entity that performs part or all of the steps in the manufacture of a licensed product or that performs a service for a Source Plasma manufacturer must register.

2. Off-Site Storage Facility

   An off-site storage facility that performs manufacturing operations, such as culling and quarantining Source Plasma products prepared for distribution, repackaging or relabeling product, and maintaining records of those operations must register.

   An off-site facility that only stores Source Plasma under specific controlled conditions, prior to shipment to a final user(s), e.g., temporary storage pending approval of a license application / supplement and distribution, is not required to register.

3. Plasma Broker

   An establishment or person that arranges the sale of Source Plasma between other entities is a broker.

   A broker that only arranges the sale or shipment of products is not required to register, but must keep appropriate records of the activities performed.

   A broker that takes possession of Source Plasma and/or engages in any manufacturing step (e.g., pooling or re-labeling products, or making aliquots) must register.

4. Source Plasma Establishment

   This is a facility licensed to collect Source Plasma, as defined in 21 CFR 640.60, for commercial distribution. The Source Plasma establishment may also collect blood and blood components for further manufacture, e.g., Red Blood Cells and/or Source Leukocytes.

5. Testing Laboratory

   A laboratory that does testing for a Source Plasma establishment; i.e., (1) required testing for evidence of a communicable disease agents, (2) donor eligibility testing, including testing for re-entry, and (3) testing to support labeling claims related to product quality must register with FDA and be either certified by the Centers for Medicare and Medicaid Services (CMS)

to perform such testing or has met equivalent requirements as determined by CMS. [21 CFR 610.40]

Note: A testing laboratory that only performs syphilis confirmatory tests is not required to register. Such testing is not required. CBER, however, encourages testing laboratories to consider registering voluntarily.

6. Other Blood Establishments

A licensed blood bank may manufacture Source Plasma, Therapeutic Exchange Plasma, or Source Leukocytes for further manufacture.

ATTACHMENT K

SOURCE LEUKOCYTES AND THERAPEUTIC EXCHANGE PLASMA

A manufacturer, blood bank, blood center, or Source Plasma establishment, may collect Source Leukocytes or Therapeutic Exchange Plasma (TEP) for further manufacture. Collection of these products is subject to the licensure provisions of Section 351 (a) of the Public Health Service Act. Manufacturers must test each product for evidence of communicable disease agents as required in 21 CFR 610.40. Lookback requirements and recommendations also apply to these products.

Inspect the manufacture of Source Leukocytes and Therapeutic Exchange Plasma under this Attachment and Compliance Program 7342.001, Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors. The deficiencies listed in Part V of this document and those in CP 7342.001 may apply to the manufacture of Source Leukocytes and Therapeutic Exchange Plasma.

A. Source Leukocytes Collection Program

A blood bank, blood center or a Source Plasma manufacturer may collect Source Leukocytes as a by-product of Whole Blood collection, by manual plasmapheresis or automated apheresis. Donors must meet the eligibility requirements for Whole Blood donation or Source Plasma donation, as appropriate to the collection method. [21 CFR 640.3, 640.63] Often, manufacturers ship Source Leukocytes prior to completing the testing required by 21 CFR 610.40, but must send consignees test results when testing is completed. CBER approves the standard operating procedures and labels for Source Leukocyte manufacture. Collection methods include the following:

1. By-product of Whole Blood Collection.

    - Donors must meet Whole Blood donor eligibility requirements. [21 CFR 640.3]
    - Collection frequency - no more frequent than once every eight weeks.

2. Manual Apheresis

    a. Single unit as a by-product of manual apheresis with no additional monitoring of the donor
        (1) Donors must meet Source Plasma donor eligibility requirements. [21 CFR 640.63]
        (2) Collection frequency - no more frequent than once every eight weeks
        (3) Manufacturers may collect Source Leukocytes only from the first unit of the 2-unit plasmapheresis collection.
    b. Single unit as a by-product of manual apheresis with additional monitoring of donor
        (1) Donors must meet Source Plasma donor eligibility requirements [21 CFR 640.63]
        (2) Collection frequency:
            (a) No more frequently than once in 48 hours or twice in a 7-day period
            (b) Total Source Leukocytes donations in one year should not exceed 32 units.
    c. Donors should have a white blood cell count of > 4000 per cubic millimeter on a blood sample tested within 7 days prior to each collection.
    d. The manufacturer may collect Source Leukocytes from one or both units of whole blood in a 2-unit plasmapheresis collection.

3. Automated Apheresis

Currently, only the Haemonetics PCS-2 is approved for automated collection of Source Leukocytes. Licensing criteria for collection of Source Leukocytes using the automated device include, but are not limited, to the following:

- Donor must meet Source Plasma donor eligibility criteria. [21 CFR 640.63]
- Collection frequency – should be no more frequent than once in a 7-day period and no more than 16 collections from a donor in one year.
- Donor should have a white blood cell count of > 4000 per cubic millimeter on a blood sample tested within 7 days prior to each collection.

Consult the following CBER guidance for additional information.
http://www.fda.gov/cber/bldmem/012881.pdf

During the inspection,
1. Review the establishment's SOPs. 2. Confirm that the firm is following its approved procedures for Source Leukocyte manufacture.

B. Therapeutic Exchange Plasma (TEP) Collection Program

Therapeutic plasmapheresis is a medical procedure for treatment of certain diseases and is carried out under a physician's order. The manufacturer removes plasma incrementally and infuses other fluids to replace the plasma. The plasma derived from these procedures is limited to the manufacture of specific in vitro diagnostic reagents for which there are no alternate source materials.

During the inspection,
1. Confirm that personnel follow the establishment's CBER-approved procedures, particularly criteria for selection of donors and the initial quarantine of product until tested for agents of communicable diseases as required by 21 CFR 610.40. 2. Donors may have a disorder that is transmissible or that is of unknown etiology. TEP is potentially hazardous; therefore, many facilities choose to quarantine it under lock and key. 3. Confirm that disposition records indicate the disposition or destruction of each container of TEP collected.

Refer to the CBER guidance at http://www.fda.gov/cber/bldmem/121484.pdf for additional Information.